STIC Search Report
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STIC Database Tracking Number: 160414

TO: Kevin Weddington **Location: REM-3A65/3C70** **Art Unit: 1614** Aug 11, 2005 **Case Serial Number: 10/783615**	**From: P. Sheppard** **Location: Remsen Building** **Phone: (571) 272-2529** **sheppard@uspto.gov**

Search Notes

REM-3C70

160414

Access DB# _____

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: K. Weddington Examiner # : 68082 Date: 7-25-05
Art Unit: 1614 Phone Number ~~30~~ 272-0587 Serial Number: 10/783,615
Mail Box and Bldg/Room Location: 3A65 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

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Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: _____

Inventors (please provide full names): Salim Yusuf

_____

Earliest Priority Filing Date: _____

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

A method of reducing diabetes with an angiotensin converting enzyme (ACE) inhibitor

Please search broadly and preferred ACE inhibitor (ramipril)

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=> d his ful

     (FILE 'HOME' ENTERED AT 14:43:38 ON 11 AUG 2005)

     FILE 'REGISTRY' ENTERED AT 14:43:56 ON 11 AUG 2005
L1             5 SEA ABB=ON  PLU=ON  RAMIPRIL/BI

     FILE 'HCAPLUS' ENTERED AT 14:44:17 ON 11 AUG 2005

     FILE 'REGISTRY' ENTERED AT 14:44:17 ON 11 AUG 2005
                SET SMARTSELECT ON
L2              SEL PLU=ON  L1 1- CHEM :       25 TERMS
                SET SMARTSELECT OFF

     FILE 'HCAPLUS' ENTERED AT 14:44:18 ON 11 AUG 2005
L3          71750 SEA ABB=ON  PLU=ON  L2
L4          71750 SEA ABB=ON  PLU=ON  L3 OR RAMIPRIL
L7         169837 SEA ABB=ON  PLU=ON  DIABETE?/CV OR ?DIABET? OR (BLD OR
                BLOOD)(2A)(SUGAR OR GLUCOSE)
L8            164 SEA ABB=ON  PLU=ON  L7(L)L4
L9           1934 SEA ABB=ON  PLU=ON  L4(L)(?MEDIC? OR ?DRUG? OR ?PHARMA? OR
                ?THERAP? OR TREATMENT OR TREATING)
L10           130 SEA ABB=ON  PLU=ON  L8 AND L9
L11            77 SEA ABB=ON  PLU=ON  L10 AND PD=<OCTOBER 21, 2002

     FILE 'REGISTRY' ENTERED AT 14:55:46 ON 11 AUG 2005
L12            8 SEA ABB=ON  PLU=ON  ANGIOTENSIN CONVERTING ENZYME?/CN

     FILE 'HCAPLUS' ENTERED AT 14:57:28 ON 11 AUG 2005

     FILE 'REGISTRY' ENTERED AT 14:57:28 ON 11 AUG 2005
                SET SMARTSELECT ON
L13             SEL PLU=ON  L12 1- CHEM :       38 TERMS
                SET SMARTSELECT OFF

     FILE 'HCAPLUS' ENTERED AT 14:57:30 ON 11 AUG 2005
L14           148 SEA ABB=ON  PLU=ON  L13
L15         23670 SEA ABB=ON  PLU=ON  L14 OR ANGIOTENSIN(W)CONVERTING(W)ENZYME?
                OR ACE
L16            69 SEA ABB=ON  PLU=ON  L15 AND L11
                D STAT QUE
                D IBIB ABS HITRN L16 1-69
L17          1994 SEA ABB=ON  PLU=ON  L15(L)L7
L22         12726 SEA ABB=ON  PLU=ON  L15(A)INHIBITOR
L25          1516 SEA ABB=ON  PLU=ON  L17 AND L22
L26         28821 SEA ABB=ON  PLU=ON  L7(L)(REDUC? OR AMEL?)
L27           807 SEA ABB=ON  PLU=ON  L25 AND L26
L28           339 SEA ABB=ON  PLU=ON  REDUC?(A)?DIABE?
L29            11 SEA ABB=ON  PLU=ON  L28 AND L27
L30             9 SEA ABB=ON  PLU=ON  L29 NOT L16
                D STAT QUE
                D IBIB ABS HITSTR L30 1-9


     FILE HOME

     FILE REGISTRY
     Property values tagged with IC are from the ZIC/VINITI data file
     provided by InfoChem.
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STRUCTURE FILE UPDATES: 10 AUG 2005 HIGHEST RN 859511-21-0
DICTIONARY FILE UPDATES: 10 AUG 2005 HIGHEST RN 859511-21-0

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 18, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

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* *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
* *
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Structure search iteration limits have been increased. See HELP SLIMITS for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

FILE HCAPLUS

FILE COVERS 1907 - 11 Aug 2005 VOL 143 ISS 7
FILE LAST UPDATED: 10 Aug 2005 (20050810/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

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=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 15:00:36 ON 11 AUG 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY (ACS)
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FILE COVERS 1907 - 11 Aug 2005  VOL 143 ISS 7
FILE LAST UPDATED: 10 Aug 2005  (20050810/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

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L1             5 SEA FILE=REGISTRY ABB=ON  PLU=ON  RAMIPRIL/BI
L2               SEL  PLU=ON  L1 1- CHEM :       25 TERMS
L3         71750 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L2
L4         71750 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L3 OR RAMIPRIL
L7        169837 SEA FILE=HCAPLUS ABB=ON  PLU=ON  DIABETE?/CV OR ?DIABET? OR
                 (BLD OR BLOOD)(2A)(SUGAR OR GLUCOSE)
L8           164 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L7(L)L4
L9          1934 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L4(L)(?MEDIC? OR ?DRUG? OR
                 ?PHARMA? OR ?THERAP? OR TREATMENT OR TREATING)
L10          130 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L8 AND L9
L11           77 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L10 AND PD=<OCTOBER 21, 2002
L12            8 SEA FILE=REGISTRY ABB=ON  PLU=ON  ANGIOTENSIN CONVERTING
                 ENZYME?/CN
L13              SEL  PLU=ON  L12 1- CHEM :       38 TERMS
L14          148 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L13
L15        23670 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L14 OR ANGIOTENSIN(W)CONVERTIN
                 G(W)ENZYME? OR ACE
L16           69 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L15 AND L11


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L16  ANSWER 1 OF 69  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2004:344319  HCAPLUS
DOCUMENT NUMBER:          141:343158
TITLE:                    Effect of ACE inhibitors on creatinine
                          clearance and albuminuria in diabetic nephropathy
AUTHOR(S):                Abdel-Salam, Mona Hosny
```

CORPORATE SOURCE: Internal Medicine Department, Ain Shams University, Egypt
SOURCE: Egyptian Journal of Hospital Medicine (**2001**), 3, 14-20
CODEN: EJHMBB
URL: http://hospitalmedicine.tripod.com/3/2.pdf
PUBLISHER: Egyptian Journal of Hospital Medicine
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English

AB 30 **Diabetic** female patients were studied for the effect of **Ramipril** on creatinine clearance and albuminuria, they all were type 2 **diabetes** mellitus and were on oral hypoglycemic **drugs.** They all had variable degrees of hypertension. **Ramipril** was taken for 3 mo in a variable doses between 5 and 10 mg/day. Creatinine clearance and albuminuria were determined before and after **treatment.** Patients were divided into 3 groups: Group 1: 10 patients with albuminuria and mild hypertension. Group 2: 10 patients with albuminuria and moderate hypertension. Group 3: 10 patients with macroalbuminuria and moderate to severe hypertension. In our study, Group 1 has made maximum benefit of **Ramipril** as regards highly significant decrease (P=.002) of creatinine clearance and of albuminuria which improved significantly (P=.001). Group 2 had a lesser success with only decrease of albuminuria significantly (P=.005) but with insignificant decrease of level of creatinine clearance. Group 3 with macroalbuminuria did not benefit from **Ramipril** effect on albuminuria but there was a significant decrease in creatinine clearance below normal levels (P=.001). Conclusion: Early and tight control of blood pressure by **Ramipril** is needed to achieve a success in **treating diabetic** nephropathy with microalbuminuria. In our study, patients with macroalbuminuria did not benefit from **Ramipril treatment.**

IT **87333-19-5, Ramipril**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**ramipril treatment** significantly decreased creatinine clearance in type 2 **diabetic** nephropathy patient with albuminuria and mild to moderate hypertension but had no effect in patient with macroalbuminuria)

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 2 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:973222 HCAPLUS
DOCUMENT NUMBER: 138:32712
TITLE: Inhibitors of the renin-angiotensin system reduce the rate of GFR decline and end-stage renal disease in patients with severe renal insufficiency
AUTHOR(S): Pisoni, Roberto; Faraone, Rita; Ruggenenti, Piero; Remuzzi, Giuseppe
CORPORATE SOURCE: Mario Negri Institute for Pharmacological Research, Unit of Nephrology and Dialysis, Ospedali Riuniti di Bergamo, Bergamo, Italy
SOURCE: Journal of Nephrology (**2002**), 15(4), 428-430
CODEN: JLNEEL; ISSN: 1121-8428
PUBLISHER: Wichtig Editore
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. **Drugs** that inhibit the renin-angiotensin system (RAS) are of proven benefit in the **treatment** of hypertension, congestive heart failure, or acute myocardial infarction. In the last

decade, several clin. trials have shown that RAS inhibitors also offer significant renoprotection in both **diabetic** and non-**diabetic** nephropathy. However, patients with advanced renal insufficiency did not take part in these trials because of the risk of acute renal failure (ARF) and hyperkalemia, and, for the same reason, most physicians do not offer these **drugs** to patients with impaired renal function. Recently, a post-hoc anal. of the **Ramipril** Efficacy In Nephropathy (REIN) study which included patients with severe renal insufficiency, showed that RAS inhibition slows glomerular filtration rate (GFR) decline over time and progression to end-stage renal disease (ESRD) in a safe way in patients quite close to ESRD (basal GFR, 10 to 30 mL/min/1.73m2). These beneficial effects have also been shown in the Reduction of Endpoints in NIDDM with the All Antagonist Losartan (RENAAL) study, in patients with type 2 **diabetes** mellitus, clin. proteinuria, and renal insufficiency, where RAS inhibition **therapy** significantly reduced the risk of ESRD once doubling of baseline serum creatinine levels had been achieved as compared to non-RAS anti-hypertensive **treatment.** Thus, these data suggest that RAS inhibition **therapy** should be given to all patients with proteinuric chronic nephropathy, independently of the level of renal function.

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 3 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:950047 HCAPLUS
DOCUMENT NUMBER: 138:19308
TITLE: Tolerability of ramipril 10 mg/day in high-risk cardiovascular Chinese patients
AUTHOR(S): Wu, Ning; Zhu, Jun Ren; Chen, Kan An
CORPORATE SOURCE: Study Investigators' Group, Peking Union Hospital, Beijing, Peop. Rep. China
SOURCE: Clinical Drug Investigation (**2002**), 22(11), 771-781
CODEN: CDINFR; ISSN: 1173-2563
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Objective: The aim of this study was to investigate the tolerability of **ramipril** 10 mg/day in high-risk cardiovascular Chinese patients, following similar criteria to those used for patient selection in the Heart Outcomes Prevention Evaluation (HOPE) study and through the collection of adverse event data by Chinese cardiologists. Design and subjects: This was a non-comparative study with single-group nonblind assessment carried out in 76 nationwide investigational sites. The target population was around 1000 patients. Men and women aged ≥55 yr were eligible for the study if they had one of the following risk factors for developing major cardiovascular events: a history of coronary artery disease, stroke, peripheral vascular disease or **diabetes** plus at least one other cardiovascular risk factor. Patients initially received **ramipril** 2.5mg tablets orally once daily, and were then titrated up to 5 mg/day and 10 mg/day at 2-wk intervals. The maintenance dosage was 10 mg/day for 1 mo. For patients with stable heart failure, the starting dosage was 1.25 mg/day, titrating up to the same maintenance dosage (10 mg/day). Adverse events were closely followed up and recorded. 981 Patients were eligible for the intention-to-treat (ITT) anal. Twenty-three patients dropped out at their own request or because of protocol violation. 958 Patients (97.7%) completed the study per protocol. Main results: 880 of 958 (91.8%) patients reached and remained at the 10 mg/day dosage level; 78 of 958 (8.1%) stayed at 5mg/day or 2.5

mg/day. 168 Patients (17.5%) had at least one adverse event. Fifty-eight patients (6.0%) stopped the **treatment** because of an adverse event; 110 (11.5%) completed the study in spite of adverse events. Altogether, 185 instances of adverse events were observed, mainly consisting of cough, dizziness, hypotension, rash and serum creatinine elevation. Most adverse events were possibly or probably related to **ramipril** . Three patients experienced serious adverse events, including one death, but investigation failed to show any evidence of a relation to **ramipril treatment.** Conclusion: **Ramipril** was well tolerated in Chinese patients with high-risk cardiovascular diseases. Patients were able to tolerate the full effective dosage level of 10 mg/day.

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 4 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:941453 HCAPLUS
DOCUMENT NUMBER: 138:19303
TITLE: The SECURE study: **treatment** with **ramipril** slows atherosclerosis, vitamin E does not
AUTHOR(S): Lonn, Eva
CORPORATE SOURCE: Hamilton Health Sciences Corporation, Hamilton, ON, Can.
SOURCE: Cardiovascular Reviews & Reports (**2002**), 23(11), 648-653
CODEN: CRRPD4; ISSN: 0197-3118
PUBLISHER: Cardiovascular Reviews & Reports, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Activation of the renin-angiotensin-aldosterone system and oxidative modification of low-d. lipoprotein cholesterol play important roles in atherosclerosis. The Study to Evaluate Carotid Ultrasound Changes in Patients Treated With **Ramipril** and Vitamin E (SECURE), a substudy of the Heart Outcomes Prevention Evaluation (HOPE) trial was a perspective, double-blind, 3+2 factorial design trial that evaluated the effects of long-term **treatment** with the **angiotensin -converting enzyme** inhibitor **ramipril** and with vitamin E on atherosclerosis progression in high-risk patients. The SECURE study enrolled 732 patients, 55 yr of age or older, with vascular disease or with **diabetes** and at least one addnl. cardiovascular risk factor who did not have heart failure or a low left ventricular ejection fraction. Patients were randomly assigned to receive **ramipril** 2.5 mg/day or **ramipril** 10 mg/day and vitamin E (RRR-α-tocopherol acetate) 400 IU/day, or their matching placebos. Average follow-up was 4.5 yr. Atherosclerosis progression was evaluated by B-mode carotid ultrasound. **Treatment** with **ramipril** was associated with a dose-dependent reduction in the atherosclerosis progression rate, while **treatment** with vitamin E had no effect on the progression of atherosclerosis. The SECURE study demonstrates that **treatment** with the high tissue-affinity **angiotensin-converting enzyme** inhibitor **ramipril** retards the progression of atherosclerosis, while vitamin E has a neutral effect on atherosclerosis progression. Results of this trial were fully concordant with the results of the parent HOPE trial, which demonstrated improved clin. outcomes in patients treated with **ramipril** but a neutral effect for vitamin E.

IT **87333-19-5, Ramipril**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)
(**ramipril treatment** slows atherosclerosis vitamin E does not in vascular disease or **diabetes** mellitus patients)
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 5 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:897760 HCAPLUS
DOCUMENT NUMBER: 137:379584
TITLE: Reduction of cardiovascular events and microvascular complications in diabetes with **ACE** inhibitor treatment: HOPE and MICRO-HOPE
AUTHOR(S): Gerstein, Hertzel C.
CORPORATE SOURCE: Department of Medicine, McMaster University, Hamilton, ON, Can.
SOURCE: Diabetes/Metabolism Research and Reviews (**2002**), 18(Suppl. 3), S82-S85
CODEN: DMRRFM; ISSN: 1520-7552
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. The Heart Outcomes Prevention Evaluation (HOPE) study, an international randomized trial, was designed to evaluate the effects of the **angiotensin-converting enzyme** (**ACE**) inhibitor **ramipril** and vitamin E in patients at high risk for cardiovascular events. The study did not detect any cardiovascular benefit or harm using vitamin E. Results for the vitamin E arm are not discussed here. Of 9541 patients, 3577 with **diabetes** received either **ramipril** (10 mg) or placebo. Among these patients, **ramipril** use was associated with a significant 25% reduction in risk for the composite endpoint of myocardial infarction (MI), stroke, or cardiovascular death after a median follow-up period of 4.5 yr. This benefit was independent of any blood pressure-lowering effect. The Microalbuminuria, Cardiovascular, and Renal Outcomes in HOPE (MICRO-HOPE) substudy in this patient population showed that **ramipril treatment** was associated with a decreased risk of development of overt nephropathy. Use of a composite measure of microvascular complications also suggested a protective effect of **ramipril treatment.** An interesting finding in the HOPE study is that **ramipril treatment** was associated with a significant 34% reduction in new diagnoses of **diabetes.** The possibility that **ACE** inhibitor **treatment** with **ramipril** may prevent new **diabetes** in non-**diabetic** patients at high risk of the disease is to be examined prospectively in the **Diabetes** Reduction Assessment with **ramipril** and rosiglitazone (DREAM) trial.
IT **87333-19-5, Ramipril**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**ACE** inhibitor **ramipril** in patients with **diabetes** at high risk for cardiovascular events)
REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 6 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:862269 HCAPLUS
DOCUMENT NUMBER: 138:104925
TITLE: Reduction of the accumulation of advanced glycation end products by **ACE** inhibition in experimental diabetic nephropathy
AUTHOR(S): Forbes, Josephine M.; Cooper, Mark E.; Thallas, Vicki;

Burns, Wendy C.; Thomas, Merlin C.; Brammar, Gail C.; Lee, Fiona; Grant, Sharon L.; Burrell, Louise A.; Jerums, George; Osicka, Tanya M.
CORPORATE SOURCE: Department of Medicine, University of Melbourne, Austin, Australia
SOURCE: Diabetes (**2002**), 51(11), 3274-3282
CODEN: DIAEAZ; ISSN: 0012-1797
PUBLISHER: American Diabetes Association
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effect of **ACE** inhibition on the formation of advanced glycation end products (AGEs) and oxidative stress was explored. Streptozocin-induced **diabetic** animals were randomized to no **treatment**, the **ACE** inhibitor **ramipril** (3 mg/L), or the AGE formation inhibitor aminoguanidine (1 g/L) and followed for 12 wk. Control groups were followed concurrently. Renal AGE accumulation, as determined by immunohistochem. and both serum and renal fluorescence, were increased in **diabetic** animals. This was attenuated by both **ramipril** and aminoguanidine to a similar degree. Nitrotyrosine, a marker of protein oxidation, also followed a similar pattern. The receptor for AGEs, gene expression of the membrane-bound NADPH oxidase subunit gp91phox, and nuclear transcription factor-κB were all increased by **diabetes** but remained unaffected by either **treatment** regimen. Two other AGE receptors, AGE R2 and AGE R3, remained unchanged for the duration of the study. The present study has identified a relationship between the renin-angiotensin system and the accumulation of AGEs in exptl. **diabetic** nephropathy that may be linked through oxidative stress.
IT **87333-19-5**, **Ramipril**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(reduction of accumulation of advanced glycation end products by **ACE** inhibition in exptl. **diabetic** nephropathy)
REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 7 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:710817 HCAPLUS
DOCUMENT NUMBER: 137:241962
TITLE: Effect of high dose ramipril with or without indomethacin on glomerular selectivity
AUTHOR(S): Pisoni, Roberto; Ruggenenti, Piero; Sangalli, Fabio; Lepre, Maria Serena; Remuzzi, Andrea; Remuzzi, Giuseppe
CORPORATE SOURCE: Clinical Research Center for Rare Diseases "Aldo & Cele Dacco", Mario Negri Institute for Pharmacological Research, Bergamo, Italy
SOURCE: Kidney International (**2002**), 62(3), 1010-1019
CODEN: KDYIA5; ISSN: 0085-2538
PUBLISHER: Blackwell Publishing, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Despite the accumulating evidence of their efficacy, **angiotensin -converting enzyme** inhibitors (ACEi) still provide imperfect renoprotection. Up-titration above conventional doses and combined **therapy** with other antiproteinuric agents may serve to achieve renoprotection in patients at risk of rapid disease progression. The effect of maximum tolerated ACEi doses (**ramipril** 15 mg/day, range 5 to 20) alone or combined with indomethacin (75 mg + 2/day) on urinary protein excretion (UPE) and glomerular barrier size-selective

function was evaluated in 19 patients with chronic non-**diabetic** nephropathies and persistent proteinuria. Maximum **ramipril** doses decreased UPE more effectively than non-ACEi **therapy.** Proteinuria reduction was associated with significant reduction (>50%) of the non-selective glomerular membrane shunt, but did not correlate with concomitant changes in arterial pressure and renal hemodynamics, nor was it influenced by **treatment** duration. The reduction in UPE and sieving coefficient of the largest neutral dextrans exceeded by twofold the reduction achieved by conventional ACEi doses in historical controls with similar renal dysfunction and proteinuria, previously studied under identical exptl. conditions. Indomethacin did not influence renal effects of maximum **ramipril** doses and was prematurely withdrawn in six patients because of reversible side effects. Serum potassium significantly increased only in combination with indomethacin and never required **treatment** withdrawal. Up-titration to maximally tolerated doses-safely increases ACEi antiproteinuric effect and may serve to achieve maximum renoprotection in the long-term. Combination with indomethacin is poorly tolerated and ineffective. Innovative approaches are needed to use ACEi more effectively.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 8 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:705991 HCAPLUS
DOCUMENT NUMBER: 137:241958
TITLE: Effect of long-term **therapy** with **ramipril** in high-risk women
AUTHOR(S): Lonn, Eva; Roccaforte, Rosa; Yi, Qilong; Dagenais, Gilles; Sleight, Peter; Bosch, Jackie; Suhan, Pamela; Micks, Mary; Probstfield, Jeffrey; Bernstein, Victoria; Yusuf, Salim
CORPORATE SOURCE: HOPE Investigators, Department of Medicine, Division of Cardiology and Population Health Institute, McMaster University, Hamilton, ON, Can.
SOURCE: Journal of the American College of Cardiology (**2002**), 40(4), 693-702
CODEN: JACCDI; ISSN: 0735-1097
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We evaluated the effects of long-term **therapy** with the **angiotensin-converting enzyme** (**ACE**) inhibitor **ramipril** on major cardiovascular (CV) outcomes in high-risk women. The effect of long-term **ACE** inhibitor **therapy** in high-risk women without heart failure and with preserved left ventricular (LV) systolic function has not been previously reported. The Heart Outcomes Prevention Evaluation (HOPE) trial is a large, randomized clin. trial that evaluated **ramipril** and vitamin E in high-risk patients. We present the preplanned anal. of the effects of **ramipril** in women in the HOPE study. The study randomized 2,480 women aged ≥55 yr with vascular disease or **diabetes** and at least one addnl. CV risk factor and without heart failure or a known low LV ejection fraction to **ramipril** (10 mg/day) or placebo. The primary outcome was the composite of myocardial infarction, stroke or CV death. Average follow-up was 4.5 yr. **Treatment** with **ramipril** resulted in reduced primary end point rates (11.3% vs. 14.9% in the placebo arm; relative risk [RR] 0.77, 95% confidence interval [CI] 0.62 to 0.96; p = 0.019), fewer strokes (3.1% vs. 4.8%; RR 0.64, 95% CI 0.43 to 0.96; p = 0.029) and fewer CV deaths (4.2% vs. 6.9%; RR 0.62, 95% CI 0.44 to 0.88; p = 0.0068). There were

trends toward reduced rates of myocardial infarction, heart failure and all-cause death. The beneficial effect of **ramipril** was similar in women and men. **Treatment** with **ramipril** reduces the CV risk in high-risk women without heart failure and with preserved LV systolic function.

REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 9 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:622240 HCAPLUS
DOCUMENT NUMBER: 137:179276
TITLE: Ramipril: a review of its use in the prevention of cardiovascular outcomes
AUTHOR(S): Warner, Gregory T.; Perry, Caroline M.
CORPORATE SOURCE: Adis International Limited, Auckland, N. Z.
SOURCE: Drugs (**2002**), 62(9), 1381-1405
CODEN: DRUGAY; ISSN: 0012-6667
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. **Ramipril**, an **angiotensin-converting enzyme** (**ACE**) inhibitor, is a **prodrug** which is rapidly hydrolyzed after absorption to the active metabolite **ramiprilat.** Earlier trials have shown that **ACE** inhibitors, when given to patients with low ejection fractions, have reduced the relative risk of myocardial infarction (MI) and other ischemic events by 14 to 23%. Subsequently, the double-blind, randomized, placebo-controlled, multicenter Heart Outcomes Prevention Evaluation (HOPE) study has shown that, in patients who are not known to have low ejection fraction or heart failure but are at increased risk for developing cardiovascular events, **ramipril** reduced the incidence of stroke, MI and death due to cardiovascular disease. Results from the HOPE study, in which 9297 patients were randomized to receive either **ramipril** 10 mg/day or placebo for a mean of 4.5 yr, indicate that **ramipril** reduced the relative risk of the composite outcome of MI, stroke and cardiovascular death by 22%. The incidence of the composite outcome was significantly lower in the **ramipril** group than in the placebo group (14.0 vs 17.8%). Patients who received **ramipril** , compared with placebo recipients, had a significantly decreased incidence of stroke, MI or death due to cardiovascular disease (3.4 vs 4.9%, 9.9 vs 12.3% and 6.1 vs 8.1%, resp.). The relative risk of death from any cause was reduced among patients who received **ramipril.** In addition, **treatment** with **ramipril** reduced as the incidence of revascularization procedures, and, among patients with **diabetes** mellitus, **ramipril** reduced the incidence of complications related to **diabetes** mellitus, including the development of overt nephropathy. Moreover, in patients without a previous diagnosis of **diabetes** mellitus, **ramipril**, compared with placebo, significantly reduced the development of **diabetes** mellitus. Furthermore, compared with patients receiving placebo, patients receiving **ramipril** had a reduced rate of progression of carotid artery wall thickness. Conclusion: **Ramipril** 10 mg/day can significantly reduce the incidence of MI, stroke or death from cardiovascular causes in patients aged ≥55 yr who are at increased risk for the development of ischemic cardiovascular events due to a history of stroke, coronary artery disease (with controlled blood pressure), **diabetes** mellitus plus at least one other risk factor or peripheral vascular disease but no heart failure or low ejection fraction. Therefore, in addition to dietary and lifestyle modifications, **ramipril** should be an integral part of secondary

prevention **therapy** in patients at increased risk for the development of cardiovascular events.

IT **87333-19-5, Ramipril**
RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of action); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**ramipril**: review of use in prevention of cardiovascular outcomes in essential hypertension, cardiovascular disease, **diabetes** mellitus, and renal dysfunction patients: reduction in myocardial infarction, stroke and cardiovascular mortality)

REFERENCE COUNT: 69 THERE ARE 69 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 10 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:469979 HCAPLUS
DOCUMENT NUMBER: 138:215053
TITLE: Results from the TIP (Tritace in Proteinuria) Intensified Monitoring Project
AUTHOR(S): Mayer, G.
CORPORATE SOURCE: TIP Study Group, Division of Nephrology, University Hospital of Innsbruck, Austria
SOURCE: Kidney & Blood Pressure Research (**2002**), 25(2), 80-86
CODEN: KBPRFC; ISSN: 1420-4096
PUBLISHER: S. Karger AG
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Albuminuria has been shown to identify patients with an increased cardiovascular risk, and in clin. studies **ACE** inhibitors reduce the urinary protein excretion. It was the primary aim of this intensified monitoring project to determine whether these results can be reproduced in a clin. practice setting. Micro- (2.7-22.6 mg albumin/mmol creatinine) or macroalbuminuria (>22.6 mg/mmol) was confirmed by a central laboratory in 598 out of 773 patients with hypertension who had albuminuria >50 mg/l on a Micral Test II performed by 147 general practitioners. Coronary heart disease (prevalence rates 15% in patients with normoalbuminuria, 33% in patients with microalbuminuria, and 40% in patients with macroalbuminuria), heart failure (prevalence rates 19, 29, and 32%, resp.), left ventricular hypertrophy (prevalence rates 30, 42, and 38%, resp.), and peripheral vascular disease (prevalence rates 7, 15, and 20%, resp.) were significantly more common in patients with elevated urinary albumin excretion. 230 patients with microalbuminuria and 202 subjects with macroalbuminuria were treated with the **angiotensin-converting enzyme** inhibitor **ramipril** for 6 mo. The **treatment** significantly lowered mean arterial blood pressure (from a median value of 120 mm Hg, quartiles 113-125 mm Hg, to 103 mm Hg, quartiles 100-109 mm Hg) as well as urinary albumin excretion (from a median value of 18 mg/mmol creatinine, quartiles 7.2-54.6 mg/mmol creatinine, to 6.5 mg/mmol creatinine, quartiles 1.6-23.1 mg/mmol creatinine). The **treatment** efficacy was unaffected by age, body mass index, and smoking status. Patients with **diabetes** mellitus type II and heart failure also had a significant, although less pronounced reduction of albuminuria. In summary, we conclude that **ramipril** is able to reduce the urinary albumin excretion in a clin. practice setting, as has been shown in clin. studies. However, the **treatment** response is not completely uniform, as special patient populations seem to be more resistant to **therapy**.

IT **87333-19-5, Ramipril**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(**ACE** inhibitor **ramipril treatment** of cardiovascular disease and effects on albuminuria)
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 11 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:369399 HCAPLUS
DOCUMENT NUMBER: 137:379502
TITLE: Clinical pharmacokinetics and selective pharmacodynamics of new **angiotensin-converting enzyme** inhibitors. An update
AUTHOR(S): Song, Jessica C.; White, C. Michael
CORPORATE SOURCE: Drug Information Center, Hartford Hospital, Hartford, CT, USA
SOURCE: Clinical Pharmacokinetics (**2002**), 41(3), 207-224
CODEN: CPKNDH; ISSN: 0312-5963
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. The **angiotensin-converting enzyme** (**ACE**) inhibitors are widely used in the management of essential hypertension, stable chronic heart failure, myocardial infarction and **diabetic** nephropathy. There is an increasing number of new agents to add to the nine **ACE** inhibitors (benazepril, cilazapril, delapril, fosinopril, lisinopril, pentopril, perindopril, quinapril and **ramipril**) reviewed in this journal in 1990. The **pharmacokinetic** properties of five newer **ACE** inhibitors (trandolapril, moexipril, spirapril, temocapril and imidapril) are reviewed in this update. All of these new agents are characterized by having carboxyl functional groups and requiring hepatic activation to form **pharmacol.** active metabolites. They achieve peak plasma concns. at times similar to those of established agents. Three of these agents (trandolapril, moexipril and imidapril) require dose redns. in patients with renal impairment. Dose redns. of moexipril and temocapril are recommended for elderly patients, and dosages of moexipril should be lower in patients who are hepatically impaired. Moexipril should be taken 1 h before meals, whereas other **ACE** inhibitors can be taken without regard to meals. The **pharmacokinetics** of warfarin are not altered by concomitant administration of trandolapril or moexipril. Although imidapril and spirapril have no effect on digoxin **pharmacokinetics**, the area under the concentration-time curve of imidapril and the peak plasma concentration of the active metabolite imidaprilat are decreased when imidapril is given with digoxin. Although six **ACE** inhibitors (captopril, enalapril, fosinopril, lisinopril, quinapril and **ramipril**) have been approved for use in heart failure by the US Food and **Drug** Administration, an overview of 32 clin. trials of **ACE** inhibitors in heart failure showed that no significant heterogeneity in mortality was found among enalapril, **ramipril**, quinapril, captopril, lisinopril, benazepril, perindopril and cilazapril. Initiation of **therapy** with captopril, **ramipril**, and trandolapril ≥3 days after an acute myocardial infarction resulted in all-cause mortality risk redns. of 18-27%. Captopril has been shown to have morbidity and mortality benefits similar to those of diuretics and β-blockers in hypertensive patients. Captopril has been shown to delay the progression of **diabetic** nephropathy, and enalapril and lisinopril prevent the development of nephropathy in normoalbuminuric patients with

diabetes. **ACE** inhibitors are generally characterized by flat dose-response curves. Lisinopril is the only **ACE** inhibitor that exhibits a linear dose-response curve. Despite the fact that most **ACE** inhibitors are recommended for once-daily administration, only fosinopril, **ramipril**, and trandolapril have trough-to-peak effect ratios >50%.

REFERENCE COUNT: 98 THERE ARE 98 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 12 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:363239 HCAPLUS
DOCUMENT NUMBER: 137:15545
TITLE: Acute and long-term effects of **ACE** inhibition on renal haemodynamics in glomerular and interstitial nephropathies
AUTHOR(S): Guidi, Ettore; Minetti, Enrico E.; Cozzi, Maria Grazia
CORPORATE SOURCE: Centro di Ricerca Clinica in Nefrologia e Ipertensione Arteriosa, Unita Operativa di Nefrologia, Dialisi e Terapia del Trapianto Renale, Ospedale Niguarda Ca'Granda, Milan, 20162, Italy
SOURCE: JRAAS (**2002**), 3(1), 40-45
CODEN: JRAAAG; ISSN: 1470-3203
PUBLISHER: JRAAS Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Angiotensin-converting enzyme** (**ACE**) inhibitors are the **drugs** of choice for the **treatment** of hypertension in patients with non-**diabetic** nephropathies. However, not every trial has reported better results with **ACE** inhibitors (**ACE**-I) than with other **drugs.** This study investigates whether the acute and chronic effects of **ACE** inhibition on renal and glomerular hemodynamics are similar in glomerular and interstitial nephropathies. The authors studied 20 hypertensive patients, on their usual diet, with mild-to-moderate chronic renal failure secondary to non-**diabetic** nephropathy. After a three-week wash out period, the authors determined plasma clearances of para-amino-hippurate and inulin before, and after acute oral administration of either enalapril or **ramipril.** This same test was carried out after one and two years of **treatment** with the same **drug.** Acute **ACE** inhibition causes a decrease of renal perfusion, glomerular filtration and pressure with an increase of afferent resistances. Long-term **ACE** inhibition is associated only with a decrease in renal perfusion, with a non-significant tendency to higher filtration fraction and lower afferent resistances. All the renal hemodynamic modifications mentioned above are present only in patients with glomerular diseases. Renal and glomerular hemodynamic responses are not similar after acute and chronic **ACE** inhibition. Only patients with glomerular diseases show acute or long-term responses to **ACE** inhibition.
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 13 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:338820 HCAPLUS
DOCUMENT NUMBER: 136:395679
TITLE: Use of ramipril in preventing stroke: double blind randomised trial
AUTHOR(S): Bosch, Jackie; Yusuf, Salim; Pogue, Janice; Sleight, Peter; Lonn, Eva; Rangoonwala, Badrudin; Davies, Richard; Ostergren, Jan

CORPORATE SOURCE: McMaster University, Hamilton, ON, L8L 2X2, Can.
SOURCE: BMJ [British Medical Journal] (**2002**), 324(7339), 699-702
CODEN: BMJBFE; ISSN: 0959-8146
PUBLISHER: BMJ Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Objective: To determine the effect of the **angiotensin converting enzyme** inhibitor **ramipril** on the secondary prevention of stroke. Design: Randomized controlled trial with 2 + 2 factorial design. Setting: 267 hospitals in 19 countries. Participants: 9297 patients with vascular disease or **diabetes** plus an addnl. risk factor, followed for 4.5 yr as part of the HOPE study. Outcome measures: Stroke (confirmed by computed tomog. or magnetic resonance imaging when available), transient ischemic attack, and cognitive function. Blood pressure was recorded at entry to the study, after 2 yr, and at the end of the study. Results: Reduction in blood pressure was modest (3.8 mm Hg systolic and 2.8 mm Hg diastolic). The relative risk of any stroke was reduced by 32% (156 v 226) in the **ramipril** group compared with the placebo group, and the relative risk of fatal stroke was reduced by 61% (17 v 44). Benefits were consistent across baseline blood pressures, **drugs** used, and subgroups defined by the presence or absence of previous stroke, coronary artery disease, peripheral arterial disease, **diabetes**, or hypertension. Significantly fewer patients on **ramipril** had cognitive or functional impairment. Conclusion: **Ramipril** reduces the incidence of stroke in patients at high risk, despite a modest reduction in blood pressure.
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 14 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:217937 HCAPLUS
DOCUMENT NUMBER: 136:334648
TITLE: What should the role of **ACE** inhibitors be in the treatment of diabetes? Lessons from HOPE and MICRO-HOPE
AUTHOR(S): Heinig, Robert E.
CORPORATE SOURCE: University of Rochester Medical School, Rochester, NY, USA
SOURCE: Diabetes, Obesity and Metabolism (**2002**), 4(Suppl. 1), S19-S25
CODEN: DOMEF6; ISSN: 1462-8902
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Exptl. and clin. evidence suggest that **angiotensin converting enzyme** (**ACE**) inhibition may reduce cardiovascular (CV) risk by directly affecting endothelial dysfunction, atherosclerosis and thrombus formation. These direct effects are in addition to effects on vascular tone or pressure. The Health Outcomes and Prevention Evaluation (HOPE) study assessed the role of an **ACE** inhibitor **ramipril** in reducing CV events in 9297 patients ≥55 yr who were at high risk of CV events but did not have left ventricular dysfunction, heart failure, or high blood pressure at the time of study entry. In the overall HOPE population, the risk of the primary composite outcome (cardiovascular death, myocardial infarction, or stroke) was reduced by 22% ($p < 0.001$), and in patients with **diabetes** plus one other CV risk, it was reduced by 25% ($p = 0.0004$). **Ramipril treatment** achieved risk reduction in patients with

mild renal insufficiency (serum creatinine ≥1.4 mg/dL). **Ramipril treatment** did not increase adverse events in patients with renal insufficiency. The Study to Evaluate Carotid Ultrasound changes in patients treated with **Ramipril** and Vitamin E (SECURE) demonstrated that **ramipril** 10 mg significantly reduced the rate of carotid intimal medial thickening, suggesting a direct effect on atherosclerotic progression.

IT **87333-19-5, Ramipril**
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antihypertensive **ACE** inhibitors role in **treatment** of hypertension, coronary artery disease, and atherosclerosis in patients with/without **diabetes** mellitus and renal insufficiency)

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 15 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:217935 HCAPLUS
DOCUMENT NUMBER: 137:122925
TITLE: Attenuating CV risk factors in patients with diabetes: clinical evidence to clinical practice
AUTHOR(S): Garber, Alan J.
CORPORATE SOURCE: Biochemistry and Molecular Biology, and Molecular and Cellular Biology, Baylor College of Medicine, Houston, TX, 77030, USA
SOURCE: Diabetes, Obesity and Metabolism (**2002**), 4(Suppl. 1), S5-S12
CODEN: DOMEF6; ISSN: 1462-8902
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Individuals with **diabetes** are at high risk of cardiovascular (CV) disease, a risk that is significantly greater in the presence of traditional CV risk factors (hyperlipidemia, hypertension, prothrombotic state). Glucose control and management of these risk factors decreases but does not eliminate CV events, reflecting the complexity of atherosclerosis. Novel risk factors (C-reactive protein, lipoprotein a, homocysteine, and endothelial dysfunction) have been proposed and are potentially modifiable. However, clin. trials data are not yet available to guide **therapy.** At this time, no single agent can achieve adequate risk reduction in patients with **diabetes.** Even with the use of multiple agents and classes of agents to manage CV risk, 75% of patients with **diabetes** are expected to die from CV causes. Despite the recent advances in primary and secondary prevention of CV events, new approaches are needed. Data from the Heart Outcomes Prevention Evaluation (HOPE) trial demonstrated that CV risk can be further reduced by the addition of the **ACE** inhibitor **ramipril** to the existing **treatment** regimen of high-risk patients with **diabetes.**

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 16 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:53704 HCAPLUS
DOCUMENT NUMBER: 136:241402
TITLE: The HOPE study and MICRO-HOPE substudy: Effects of **ramipril** on cardiovascular and microvascular outcomes in people with **diabetes** mellitus
AUTHOR(S): Patel, Vinod; Panja, Srinivas; Venkataraman, Asok

CORPORATE SOURCE: Diabetes and Endocrinology Centre, George Eliot Hospital NHS Trust, Nuneaton, CV10 7DJ, UK
SOURCE: British Journal of Diabetes & Vascular Disease (**2001**), 1(1), v4-45,48,50-51
CODEN: BJDVAI; ISSN: 1474-6514
PUBLISHER: MediNews (Diabetes) Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A study provides a clin. summary of the heart outcomes prevention evaluation (HOPE) study and the MICRO-HOPE substudy, and suggests recommendations for clin. study. The HOPE study attempts to determine whether **ACE** inhibitor **treatment** with **ramipril** in high-risk patients with **diabetes** lowers the risk of cardiovascular events. On the other hand, MICRO-HOPE substudy investigated the effect of **ACE** inhibitor **treatment** with **ramipril** on microalbuminaria and **diabetic** retinopathy. All **diabetes** programs should aim to decrease cardiovascular disease by an aggressive strategy to reduce blood pressure to the target of 140/80 mmHg or lower, improve glycemic control to a target HbA1C of 7% or lower, lipid lowering, smoking cessation, aspirin **treatment**, together with due attention to healthy eating, exercise and weight reduction The HOPE and MICRO-HOPE study clearly exhibited the beneficial effect of adding an **ACE** inhibitor into this strategy.

IT **87333-19-5**, **Ramipril**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**ramipril** effect on cardiovascular and microvascular outcomes in people with **diabetes** mellitus)

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 17 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:37832 HCAPLUS
DOCUMENT NUMBER: 137:3811
TITLE: Renin-angiotensin system, proteinuria, and tubulointerstitial damage
AUTHOR(S): Ruggenenti, Piero; Aros, Claudio; Remuzzi, Giuseppe
CORPORATE SOURCE: Mario Negri Institute for Pharmacological Research, Ospedali Riuniti di Bergamo, Italy
SOURCE: Contributions to Nephrology (**2001**), 135(Renin-Angiotensin System and Progression of Renal Diseases), 187-199
CODEN: CNEPDD; ISSN: 0302-5144
PUBLISHER: S. Karger AG
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review discusses the pathophysiol. of proteinuric renal disease, focusing on the role of renin-angiotensin system (RAS). Clin. evidence of the renoprotective effects of **angiotensin-converting enzyme** (**ACE**) inhibitors in patients with **diabetic** and non-**diabetic** chronic renal disease is presented. The REIN (**ramipril** efficacy in nephropathy) core study demonstrated that, at comparable levels of blood pressure control, **ACE** inhibitors are more effective than conventional antihypertensive **therapy** in reducing proteinuria, slowing glomerular filtration rate decline, and limiting progression to end-stage renal disease.

REFERENCE COUNT: 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 18 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:4211 HCAPLUS
DOCUMENT NUMBER: 136:193991
TITLE: **ACE** inhibitors to prevent end-stage renal disease: when to start and why possibly never to stop: a post hoc analysis of the REIN trial results
AUTHOR(S): Ruggenenti, Piero; Perna, Annalisa; Remuzzi, Giuseppe
CORPORATE SOURCE: Mario Negri Institute for Pharmacological Research, Clinical Research Center for Rare Diseases, Ranica, Italy
SOURCE: Journal of the American Society of Nephrology (**2001**), 12(12), 2832-2837
CODEN: JASNEU; ISSN: 1046-6673
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In this post hoc, secondary anal. of the **Ramipril** Efficacy In Nephropathy (REIN) trial, an **angiotensin-converting enzyme** (**ACE**) inhibition risk/benefit profile was assessed in 322 patients with **nondiabetic**, proteinuric chronic nephropathies and different degrees of renal insufficiency. The rate of GFR decline (ΔGFR) and the incidence of end-stage renal disease (ESRD) during **ramipril** or non-**ACE** inhibitor **treatment** were compared within three tertiles of basal GFR. ΔGFR was comparable in the three tertiles, whereas the incidence of ESRD was higher in the lowest tertile than in the middle and highest tertiles. **Ramipril** decreased ΔGFR by 22%, 22%, and 35% and the incidence of ESRD by 33% ($P < 0.05$), 37%, and 100% ($P < 0.01$) in the lowest, middle, and highest tertiles, resp. ΔGFR reduction was predicted by basal systolic ($P < 0.0001$), diastolic ($P = 0.02$), and mean ($P < 0.001$) BP and proteinuria ($P < 0.0001$) but not by basal GFR ($P = 0.12$). ESRD risk reduction was predicted by basal proteinuria ($P < 0.01$) and GFR ($P < 0.0001$) and was strongly dependent on **treatment** duration ($P < 0.0001$). Adverse events were comparable among the three tertiles and within each tertile in the two **treatment** groups. Thus, disease progression and response to **ACE** inhibition do not depend on severity of renal insufficiency. The risk of ESRD and the absolute number of events saved by **ACE** inhibition is highest in patients with the lowest GFR. However, renoprotection is maximized when **ACE** inhibition is started earlier and when long-lasting **treatment** may result in GFR stabilization and definitive prevention of ESRD.
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 19 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:908781 HCAPLUS
DOCUMENT NUMBER: 136:177727
TITLE: The effects of an **ACE** inhibitor and a calcium antagonist on the progression of renal disease: The nephros study
AUTHOR(S): Herlitz, Hans; Harris, Kevin; Rister, Teut; Boner, Geoffrey; Bernheim, Jacques; Chanard, Jacques; Aurell, Matuas
CORPORATE SOURCE: Department of Nephrology, Sahlgrenska Hospital, Goteborg University, Swed.
SOURCE: Nephrology, Dialysis, Transplantation (**2001**), 16(11), 2158-2165
CODEN: NDTREA; ISSN: 0931-0509
PUBLISHER: Oxford University Press

DOCUMENT TYPE: Journal
LANGUAGE: English
AB The renoprotective effect of **ACE** inhibition in chronic renal disease is well established but the studies on effects of calcium antagonists on progression of renal disease and on proteinuria have given results. We conducted an open long-term randomized prospective multi-center study comparing the combination of **ramipril** (R) and felodipine ER (F) with either **drug** alone in non-**diabetic** renal disease. Included were patients with uncontrolled hypertension (diastolic blood pressure (DBP)) ≥ 95 mmHg on **treatment** with a diuretic and a beta-blocker. Fifty-one patients received the combination of R and F, 54 patients R, and 53 patients F. The **treatment** goal was a DBP < 90 mmHg and a similar BP reduction in the three groups. Mean doses at the last visit were 5+5, 10 and 9 mg, resp., after a mean **treatment** time of nearly 2 yr. The progression of renal impairment was studied by serial measurements of serum creatinine, iohexol clearance, and albuminuria. The reduction in supine systolic (S) BP and DBP expressed as median values were -19.0/-14.5, -14.3/-15.0 and -13.5/-13.3 mmHg in the R + F, R, and F groups, resp. There was no significant difference between the groups. When correction for the acute **drug** effect was performed the R + F group had a slower progression rate of the renal disease (loss of glomerular filtration rate (GFR) ml/min/yr) compared with the F group ($P < 0.05$) but not to the R group ($P > 0.20$). There was a rise in albuminuria after 2 yr in the F group ($P < 0.05$), but no change was found in the other groups. In patients with non-**diabetic** renal disease the combination of an **ACE** inhibitor and a calcium antagonist in reduced doses used in addition to baseline **therapy** with beta-blockers and diuretics, tended to cause a better BP reduction as each **drug** per se. The R + F **treatment** also caused a slower progression of the renal disease compared with F alone. The combination **treatment** seems to afford better BP control and appears to be a favorable **therapeutic** option in patients with renal disease and hypertension.
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 20 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:768085 HCAPLUS
DOCUMENT NUMBER: 136:112497
TITLE: **Ramipril** and the development of **diabetes**
AUTHOR(S): Yusuf, Salim; Gerstein, Hertzel; Hoogwerf, Byron; Pogue, Janice; Bosch, Jackie; Wolffenbuttel, Bruce H. R.; Zinman, Bernard
CORPORATE SOURCE: McMaster Univ., Hamilton, Can.
SOURCE: JAMA, the Journal of the American Medical Association (**2001**), 286(15), 1882-1885
CODEN: JAMAAP; ISSN: 0098-7484
PUBLISHER: American Medical Association
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Context: Type 2 **diabetes** is a growing clin. and public health problem. Preventive efforts related to lifestyle modification are not always successful; therefore, alternative prevention strategies need to be studied. Objective: To investigate the effectiveness of **ramipril**, an **angiotensin-converting enzyme** inhibitor, in preventing **diabetes** among high-risk persons. Design, Setting, and Participants: The randomized, controlled Heart Outcomes Prevention Evaluation trial of 5720 patients older than 55 yr without known **diabetes** but with vascular disease who were

followed up for a mean of 4.5 yr. The study included 267 hospitals in 19 countries and was conducted between 1994 and 1999. Intervention: Patients were randomly assigned to receive **ramipril**, up to 10 mg/d (n=2837), or placebo (n=2883). Main Outcome Measure: Diagnosis of **diabetes** determined from self-report at follow-up visits every 6 mo, compared between the 2 groups. Results: One hundred and two individuals (3.6%) in the **ramipril** group developed **diabetes** compared with 155 (5.4%) in the placebo group (relative risk [RR], 0.66; 95% confidence interval [CI], 0.51-0.85, P <.001). Similar results were noted when different diagnostic criteria were used; in the **ramipril** group, the RR for diagnosis of **diabetes** and Hb A1c greater than 110% was 0.60 (95% CI, 0.43-0.85), for initiation of glucose-lowering **therapy**, 0.56 (95% CI, 0.41-0.77), and for both, 0.51 (95% CI, 0.34-0.76). These effects were also consistently seen in several subgroups examined Conclusions: **Ramipril** is associated with lower rates of new diagnosis of **diabetes** in high-risk individuals. Because these results have important clin. and public health implications, this hypothesis requires prospective confirmation.

IT **87333-19-5**, **Ramipril**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**ramipril** role in prevention of **diabetes** in high-risk humans)

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 21 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:567029 HCAPLUS
DOCUMENT NUMBER: 135:326840
TITLE: Is **ramipril** the pril for **diabetes** and kidney disease?
AUTHOR(S): Doggrell, Sheila A.
CORPORATE SOURCE: Doggrell Biomedical Communications, Auckland, N. Z.
SOURCE: Drugs of Today (**2001**), 37(5), 321-331
CODEN: MDACAP; ISSN: 0025-7656
PUBLISHER: Prous Science
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with refs. **Ramipril** is safe and effective in the **treatment** of hypertension and heart failure, but this is not reviewed here. **Ramipril** is a lipophilic **angiotensin-converting enzyme** inhibitor suitable for once-daily administration. In addition to decreasing angiotensin II and increasing bradykinin levels, **ramipril** increases the levels of vasodilatory renal medullary neutral lipids and inhibits platelet-derived growth factor-induced proliferation of glomerulus cells. **Ramipril** also decreases transforming growth factor-β in the kidney. Changes in kidney structure and proteinuria are characteristics of the streptozotocin (STZ) rat model of **diabetes**, and these are prevented by **ramipril**. In STZ **diabetes**, doses of **ramipril** that have no effect on blood pressure reverse vascular hypertrophy. In animal models of kidney failure (subtotal nephrectomy, stroke-prone spontaneously hypertensive rats), **ramipril** is reno-protective and some of this renoprotective effect is independent of blood pressure lowering. In humans, clin. doses of **ramipril** probably do not modify glucose metabolism but do reduce the levels of LDL- and HDL-cholesterol. In clin. trials of renal effects, **ramipril** has been shown to increase cortical nephron flow in hypertension and to reduce proteinuria in patients with and without **diabetes** and/or hypertension. Some of the smaller clin. trials showed beneficial effects

on kidney function with low doses of **ramipril** that do not lower blood pressure. A large clin. trial in **nondiabetic** proteinuria, the **Ramipril** Efficacy in Nephropathy (REIN) trial, has shown that **ramipril** 1.25 mg/day, which does not lower blood pressure, arrested the decline in glomerular filtration rate and prolonged the time to end-stage renal failure. In **diabetic** patients who have had a previous cardiovascular event or having one other cardiovascular risk factor, the MICRO-HOPE clin. trial showed that **ramipril** lowers the combined risk of myocardial infarction, stroke and cardiovascular death by 25%. In conclusion, **ramipril** has proven beneficial effects in kidney disease alone or in association with **diabetes** and in **diabetes** without kidney disease, and is the pril for **diabetes** and kidney disease.

IT **87333-19-5, Ramipril**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antihypertensive and kidney sparing effects of **ramipril** in human **diabetes**)

REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 22 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:537151 HCAPLUS
DOCUMENT NUMBER: 135:330009
TITLE: Impaired angiotensin II regulation of renal C-type natriuretic peptide mRNA expression in experimental diabetes mellitus
AUTHOR(S): Walther, T.; Schuitheiss, H.-P.; Tschope, C.
CORPORATE SOURCE: Department of Cardiology and Pneumology, University Hospital Benjamin Franklin, Free University of Berlin, Berlin, D-12200, Germany
SOURCE: Cardiovascular Research (**2001**), 51(3), 562-566
CODEN: CVREAU; ISSN: 0008-6363
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Objective: Abnormalities in the regulation of natriuretic peptides (NP) associated with major diseases such as hypertension, heart failure, and **diabetes** mellitus (DM) have been reported. We investigated levels of mRNA for the vasodilator C-type natriuretic peptide (CNP) in the renal cortex of streptozotocin (STZ)-**diabetic** rats and the influence of an angiotensin II inhibition. Methods: DM was induced in Wistar rats by a single STZ injection. Rats were kept for 12 wk. Addnl., the influence of the **ACE** inhibitor **ramipril** (Ram: 3 mg/kg/day) and the AT1 receptor antagonist losartan (Los: 20 mg/kg/day) on CNP expression in the STZ-**diabetic** and control groups was studied (each group n=6). Animals were characterized by their mean arterial **blood** pressure, plasma **glucose** levels, and renal function (each group n=9). After extraction of total renal cortical RNA, CNP expression was analyzed by Northern blots. Results: Renal function was impaired in STZ-**diabetic** rats which has been improved by Ram and Los **treatment.** Untreated STZ-**diabetic** rats showed no difference in renal CNP expression compared to untreated controls. Ram and Los **treatments** led to an increase in renal cortical CNP mRNA in both **diabetic** and non-**diabetic** rats. This effect was weaker in STZ-**diabetic** rats (Ram: control 5.4-fold, STZ 3.5-fold; Los: control 4.2-fold, STZ 1.9-fold). Conclusion: These results clearly demonstrate a direct regulatory effect of the renin-angiotensin

system (RAS) on renal mRNA levels of CNP. We suggest that RAS inhibition not only prevents the generation of angiotensin II (AngII) but also leads to a stimulation of CNP expression. We conclude that AngII suppresses CNP expression via the AT1 receptor and this mechanism is impaired in STZ-**diabetic** rats.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 23 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:489221 HCAPLUS
DOCUMENT NUMBER: 135:71295
TITLE: Novel method of diabetes treatment using insulin sensitizers
INVENTOR(S): Buckingham, Robin Edward
PATENT ASSIGNEE(S): Smithkline Beecham P.L.C., UK
SOURCE: PCT Int. Appl., 12 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001047509	A2	20010705	WO 2000-GB5006	20001222 <--
WO 2001047509	A3	20020912		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1261373	A2	20021204	EP 2000-987579	20001222
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003518493	T2	20030610	JP 2001-548104	20001222
US 2003060489	A1	20030327	US 2002-168872	20021004
US 2004176373	A1	20040909	US 2004-803300	20040318

PRIORITY APPLN. INFO.:

GB 1999-30688	A	19991224
GB 1999-30689	A	19991224
GB 1999-30690	A	19991224
GB 1999-30692	A	19991224
WO 2000-GB5006	W	20001222
US 2002-168872	A1	20021004

AB A method for the treatment of diabetes mellitus, especially type II diabetes and the cardiac conditions associated with diabetes mellitus in a mammal such as a human, comprises administering an effective non-toxic and pharmaceutically acceptable amount of an insulin sensitizer, such as 5[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, and an agent used in the treatment of the cardiac conditions associated with diabetes mellitus.

IT **87333-19-5**, **Ramipril**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thiazolidine insulin sensitizer and cardiovascular agents for

treatment of **diabetes** and related cardiac conditions)

L16 ANSWER 24 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:449567 HCAPLUS
DOCUMENT NUMBER: 135:266906
TITLE: Cost effectiveness of **ramipril** in patients with non-**diabetic** nephropathy and hypertension. Economic evaluation of **Ramipril** Efficacy In Nephropathy (REIN) study for Germany from the perspective of statutory health insurance
AUTHOR(S): Schadlich, Peter K.; Brecht, Josef Georg; Brunetti, Massimo; Pagano, Eva; Rangoonwala, Badrudin; Huppertz, Eduard
CORPORATE SOURCE: Outcomes Research and Health Economics, InForMed GmbH - Outcomes Research and Health Economics, Ingolstadt, Germany
SOURCE: PharmacoEconomics (**2001**), 19(5, Pt. 1), 497-512
CODEN: PARMEK; ISSN: 1170-7690
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In the **Ramipril** Efficacy In Nephropathy (REIN) trial, **ramipril** significantly lowered the rate of reaching the combined end-point of doubling of baseline serum creatinine levels or end-stage renal failure (ESRF). To determine the addnl. cost per patient-year of chronic (long term) dialysis avoided (PYCDA) when the **ACE** inhibitor, **ramipril**, was added to conventional **treatment** of patients with non-**diabetic** nephropathy and hypertension. Statutory Health Insurance (SHI) provider in Germany. Data from the REIN Study were used in a cost-effectiveness anal. (CEA). A modeling approach was used, which was based on secondary anal. of published data, and costs were those incurred by the SHI provider (i.e. SHI expenses). In the base-case anal., average case-related SHI expenses were applied and PYCDA were quantified using the cumulative incidence of ESRF as observed in the REIN trial. The incremental cost-effectiveness ratios (ICERs) of **ramipril** varied between about -76 700 deutschmarks (DM) and -DM81 900 per PYCDA (DM1 ≈0.55 US dollars; 1999 values), according to the **treatment** periods of 1 yr and 3 yr, resp. In the sensitivity anal., the robustness of the model and its results were shown when the extent of influence of different model variables on the base-case results was investigated. First, probabilities of ESRF and PYCDA were estimated according to the Weibull method. Second, the influence of the model variables on the target variable was quantified using a deterministic model. Third, the dependency of the target variable (ICER) on random variables was described in a simulation. The cost for chronic dialysis had by far the greatest impact on the target variable, which was 28 times greater than the impact of clin. effectiveness of **ramipril**, i.e. the number of PYCDA. There were net savings per PYCDA with **ramipril** **treatment** after 1, 2 and 3 yr: 95% of the 10 000 simulation steps resulted in savings of between DM69 500 and DM94 600 per PYCDA after 3 yr. Results from this evaluation show that **ramipril** offers enormous savings from the perspective of the SHI provider (third-party payer) in Germany when added to the conventional **treatment** of patients with non-**diabetic** nephropathy and hypertension.

IT **87333-19-5**, **Ramipril**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cost effectiveness of **ramipril** in humans with non-

diabetic nephropathy and hypertension)
REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 25 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:384801 HCAPLUS
DOCUMENT NUMBER: 135:236157
TITLE: Reduction of **ACE** activity is insufficient to decrease microalbuminuria in normotensive patients with type 1 diabetes
AUTHOR(S): Bojestig, Mats; Kariberg, Bengt E.; Lindstrom, Torbjorn; Nystrom, Fredrik H.
CORPORATE SOURCE: Department of Medicine and Care, University Hospital of, Linkoping, SE-581 85, Swed.
SOURCE: Diabetes Care (**2001**), 24(5), 919-924
CODEN: DICAD2; ISSN: 0149-5992
PUBLISHER: American Diabetes Association, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The objective of this study was toexamine whether administration of 1.25 and 5.0 mg **ramipril** daily, compared with placebo **treatment**, reduces the urinary albumin excretion rate (UAER) in normotensive patients with type 1 **diabetes. Ramipril** was administered double blind at two different doses (1.25 [n = 19] and 5.0 mg [n = 18]), and compared with placebo (n = 18) after a single-blind placebo period of 1-4 wk. The patients (total, n = 55; women, n = 14) were followed for 2 yr. To document an effect on the renin-angiotensin system, **ACE** activity and plasma-renin activity (PRA) were measured. In addition, 24-h ambulatory blood pressure (BP) was recorded at baseline and repeated after 1 and 2 yr using a Spacelab 90207 ambulatory BP recording device (Spacelab, Redmont, CA). Both doses of **ramipril** were sufficient to reduce **ACE** activity and to increase PRA significantly as compared with placebo ($P < 0.05$ for both). On the other hand, neither ambulatory nor clinic BP was affected by either dose of **ramipril** compared with the placebo group. There was no progression of UAER in the placebo group during the 2 yr of the study. Anal. of covariance showed no differences in UAER between the three **treatment** groups at year 1 ($P = 0.94$) or year 2 ($P = 0.97$), after adjusting for baseline. Furthermore, there were no statistically significant changes from baseline UAER within any of the three **treatment** groups. **Treatment** with **ramipril** did not affect microalbuminuria or clinic or ambulatory BP in this study. On the basis of the present study, we question the clin. use of **ACE** inhibitors in stably normotensive patients with type 1 **diabetes** and microalbuminuria in whom a concomitant reduction in BP is not demonstrated.
IT **87333-19-5, Ramipril**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**ramipril** as **ACE** inhibitor did not decrease microalbuminuria in humans with type 1 **diabetes** and normotension)
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 26 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:349518 HCAPLUS
DOCUMENT NUMBER: 135:221014
TITLE: Renal insufficiency as a predictor of cardiovascular

outcomes and the impact of ramipril: the HOPE randomized trial

AUTHOR(S): Mann, Johannes F. E.; Gerstein, Hertzel C.; Pogue, Janice; Bosch, Jackie; Yusuf, Salim

CORPORATE SOURCE: McMaster University, Hamilton, ON, L8L 2X2, Can.

SOURCE: Annals of Internal Medicine (**2001**), 134(8), 629-636
CODEN: AIMEAS; ISSN: 0003-4819

PUBLISHER: American College of Physicians-American Society of Internal Medicine

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Background: The cardiovascular risk associated with early renal insufficiency is unknown. Clinicians are often reluctant to use **angiotensin-converting enzyme** inhibitors in patients with renal insufficiency. Objective: To determine whether mild renal insufficiency increases cardiovascular risk and whether **ramipril** decreases that risk. Design: Post hoc anal. Setting: The Heart Outcomes and Prevention Evaluation (HOPE) study, a randomized, double-blind, multinational trial involving 267 study centers. Patients: 980 patients with mild renal insufficiency (serum creatinine concentration ≥ 124 μmol/L [≥1.4 mg/dL]) and 8307 patients with normal renal function (serum creatinine concentration < 124 μmol/L [<1.4 mg/dL]). Measurements: The primary outcome measure was incidence of cardiovascular death, myocardial infarction, or stroke. Results: Cumulative incidence of the primary outcome was higher in patients with renal insufficiency than in those without (22.2% vs. 15.1%; P < 0.001) and increased with serum creatinine concentration Patients with renal insufficiency had a substantially increased risk for cardiovascular death (11.4% vs. 6.6%) and total mortality (17.8% vs. 10.6%) (P < 0.001 for both comparisons). The effect of renal insufficiency on the primary outcome (adjusted hazard ratio, 1.40 [95% Cl, 1.16 to 1.69]) was independent of known cardiovascular risks and **treatment**. **Ramipril** reduced the incidence of the primary outcome in patients with and those without renal insufficiency (hazard ratio, 0.80 vs. 0.79; P > 0.2 for the difference). Conclusions: In patients who had preexisting vascular disease or **diabetes** combined with an addnl. cardiovascular risk factor, mild renal insufficiency significantly increased the risk for subsequent cardiovascular events. **Ramipril** reduced cardiovascular risk without increasing adverse effects.

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 27 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2001:249206 HCAPLUS

DOCUMENT NUMBER: 135:190185

TITLE: Aminoguanidine and **ramipril** prevent **diabetes**-induced increases in protein kinase C activity in glomeruli, retina, and mesenteric artery

AUTHOR(S): Osicka, Tanya M.; Yu, Yunxia; Lee, Vincent; Panagiotopoulos, Sianna; Kemp, Bruce E.; Jerums, George

CORPORATE SOURCE: Endocrine Unit, University of Melbourne, Victoria, 3065, Australia

SOURCE: Clinical Science (**2001**), 100(3), 249-257
CODEN: CSCIAE; ISSN: 0143-5221

PUBLISHER: Portland Press Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB This study investigated the effects of insulin **therapy**,

inhibition of advanced glycation end-product formation with aminoguanidine and **angiotensin-converting enzyme** inhibition with **ramipril** on **diabetes**-related increases in protein kinase C (PKC) activity in the streptozotocin-**diabetic** rat. PKC activity in the glomeruli, retina, and mesenteric artery was increased by 1.5-2-fold after induction of **diabetes**, and this increase was maintained over 24 wk. **Treatment** with insulin at 2 units or 6 units per day attenuated glomerular PKC in proportion to the level of glycoHb after 4 wk of **diabetes**. The higher dose of insulin prevented the **diabetes**-related increase in glomerular PKC activity, although **blood glucose** levels were not normalized. After 8 wk of **diabetes**, **ramipril** completely prevented the **diabetes**-related increases in PKC activity in the glomeruli, retina, and mesenteric artery. By contrast, aminoguanidine **treatment** resulted in no inhibition of glomerular PKC activity, partial inhibition of retinal PKC activity and complete inhibition of mesenteric artery PKC activity. After 24 wk of **diabetes**, both aminoguanidine and **ramipril** prevented the **diabetes**-related increases in PKC activity in all 3 tissues, in parallel with suppression of albuminuria by both agents. Aminoguanidine also prevented **diabetes**-related increases in retinal permeability at 16 wk. These results suggest that the organ-protective effects of insulin, aminoguanidine, and **ramipril** in **diabetes** may be mediated, at least in part, through the differential inhibition of PKC activity in various tissues.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 28 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:224868 HCAPLUS
DOCUMENT NUMBER: 135:174983
TITLE: Effects of ramipril and vitamin E on atherosclerosis. The study to evaluate carotid ultrasound changes in patients treated with ramipril and vitamin E (SECURE)
AUTHOR(S): Lonn, Eva M.; Yusuf, Salim; Dzavik, Vladimir; Doris, C. Ian; Yi, Qilong; Smith, Sandra; Moore-Cox, Anne; Bosch, Jackie; Riley, Ward A.; Teo, Koon K.
CORPORATE SOURCE: Departments of Medicine, McMaster University, Hamilton, ON, Can.
SOURCE: Circulation (**2001**), 103(7), 919-925
CODEN: CIRCAZ; ISSN: 0009-7322
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Background-Activation of the renin-angiotensin-aldosterone system and oxidative modification of LDL cholesterol play important roles in atherosclerosis. The Study to Evaluate Carotid Ultrasound changes in patients treated with **Ramipril** and vitamin E (SECURE), a substudy of the Heart Outcomes Prevention Evaluation (HOPE) trial, was a prospective, double-blind, 3 X 2 factorial design trial that evaluated the effects of long-term **treatment** with the **angiotensin-converting enzyme** inhibitor **ramipril** and vitamin E on atherosclerosis progression in high-risk patients. Methods and Results-A total of 732 patients ≥55 yr of age who had vascular disease or **diabetes** and at least one other risk factor and who did not have heart failure or a low left ventricular ejection fraction were randomly assigned to receive **ramipril** 2.5 mg/d or 10 mg/d and vitamin E (RRR-α-tocopheryl acetate) 400 IU/d or their matching placebos. Average follow-up was 4.5 yr. Atherosclerosis progression was evaluated by B-mode carotid ultrasound. The progression slope of the mean

maximum carotid intimal medial thickness was 0.0217 mm/yr in the placebo group, 0.0180 mm/yr in the **ramipril** 2.5 mg/d group, and 0.0137 mm/yr in the **ramipril** 10 mg/d group (P=0.033). There were no differences in atherosclerosis progression rates between patients on vitamin E and those on placebo. Conclusions-Long-term **treatment** with **ramipril** had a beneficial effect on atherosclerosis progression. Vitamin E had a neutral effect on atherosclerosis progression.

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 29 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:167787 HCAPLUS
DOCUMENT NUMBER: 134:202715
TITLE: Pharmaceutical formulations of **ACE** and ATII inhibitors for prevention of stroke, diabetes and/or congestive heart failure
INVENTOR(S): Schoelkens, Bernward; Bender, Norbert; Rangoonwala, Badrudin; Dagenais, Gilles; Gerstein, Hertzel; Ljunggren, Anders; Yusuf, Salim
PATENT ASSIGNEE(S): Aventis Pharma Deutschland G.m.b.H., Germany
SOURCE: PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001015673	A2	20010308	WO 2000-EP8341	20000825 <--
WO 2001015673	A3	20020307		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2382387	AA	20010308	CA 2000-2382387	20000825 <--
CA 2382387	C	20010308		
CA 2500709	AA	20010308	CA 2000-2500709	20000825 <--
BR 2000013540	A	20020430	BR 2000-13540	20000825 <--
EP 1212081	A2	20020612	EP 2000-965898	20000825 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
TR 200200518	T2	20020621	TR 2002-200200518	20000825 <--
TR 200202466	T2	20021223	TR 2002-200202466	20000825
TR 200202467	T2	20021223	TR 2002-200202467	20000825
JP 2003508426	T2	20030304	JP 2001-519887	20000825
EE 200200085	A	20030415	EE 2002-85	20000825
EP 1437131	A1	20040714	EP 2004-6330	20000825
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
BG 106319	A	20021229	BG 2002-106319	20020118
NO 2002000850	A	20020221	NO 2002-850	20020221 <--
ZA 2002001471	A	20030303	ZA 2002-1471	20020221
PRIORITY APPLN. INFO.:			SE 1999-3028 A	19990827

CA 2000-2382387 A3 20000825
EP 2000-965898 A3 20000825
WO 2000-EP8341 W 20000825

AB The present invention relates to use of an inhibitor of the renin-angiotensin system (RAS), i.e., inhibitors of **angiotensin-converting enzyme** (**ACE**) and angiotensin II type 1 receptor (ATII) antagonists or a **pharmaceutically** acceptable derivative thereof, particularly **ramipril** or **ramiprilat**, in the manufacture of a **medicament** for the prevention and/or **treatment** of stroke, **diabetes** and/or congestive heart failure (CHF). A large-scale clin. trial was designed to examine the effect of the **ACE** inhibitor **ramipril** vs. placebo in reducing cardiovascular events. There was a clear 32% reduction in the **ramipril** group in the number of patients who developed a stroke, and this is surprising since patients were normotensive when recruited to the study. The number of patients who developed CHF was significantly reduced by 21% in the **ramipril** group, which is unexpected since patients had no signs or symptoms of CHF at study start. Equally surprising is the marked 36% reduction in the number of patients who developed **diabetes** in the **ramipril** group.

IT **87269-97-4**, **Ramiprilat 87333-19-5**, **Ramipril**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. of inhibitors of renin-angiotensin system for prevention and/or **treatment** of stroke, **diabetes** and/or congestive heart failure)

L16 ANSWER 30 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:885303 HCAPLUS
DOCUMENT NUMBER: 135:86794
TITLE: Low-dose **ramipril** reduces microalbuminuria in type 1 **diabetic** patients without hypertension: results of a randomized controlled trial
CORPORATE SOURCE: The ATLANTIS Study Group, USA
SOURCE: Diabetes Care (**2000**), 23(12), 1823-1829
CODEN: DICAD2; ISSN: 0149-5992
PUBLISHER: American Diabetes Association, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB OBJECTIVE: To assess if low (1.25 mg) and/or standard (5 mg) doses of the **ACE** inhibitor **ramipril** could prevent progression of microalbuminuria (incipient **diabetic** nephropathy) in normotensive type 1 **diabetic** patients. RESEARCH DESIGN AND METHODS: This study, using a multicenter randomized placebo-controlled double-blind parallel group, was conducted over 2 yr in 28 outpatient **diabetic** clinics in the U.K. and Ireland. We screened 334 type 1 **diabetic** patients with suspected microalbuminuria and normal blood pressure; of these, 140 patients 18-65 yr of age with a diagnosis of type 1 **diabetes** and persistent microalbuminuria, defined as urinary albumin excretion rate (AER) of 20-200 μg/min, were enrolled in the study. RESULTS: The proportion of patients progressing to macroalbuminuria was reduced in the **ramipril** groups but did not reach statistical significance over 2 yr. AER was significantly lower at year 2 in the combined **ramipril**-treated patients vs. placebo ($P = 0.013$). More patients on **ramipril** regressed to normoalbuminuria (<20 μg/min), with 11% for 1.25 mg **ramipril**, 20% for 5 mg **ramipril**, and 4% for placebo ($P = 0.053$). Blood pressure was significantly reduced to a similar extent with both 1.25 and

5 mg **ramipril**. Supine systolic blood pressure increased from 130 to 134 mmHg in the placebo group and fell in the 1.25 mg **ramipril** group (from 132 to 129 mmHg) and in the 5 mg **ramipril** group (from 134 to 130 mmHg) (P = 0.003, compared with placebo). No statistically significant changes were observed in glomerular filtration rate (GFR) between the placebo-and **ramipril**-treated groups during the 2-yr period. CONCLUSIONS: Microalbuminuria is reduced significantly by **ramipril treatment** in type 1 **diabetic** patients without hypertension. Although the magnitude of the response was greater, there is no significant difference between responses to 1.25 or 5 mg **ramipril**. Small but highly significant redns. in systolic and mean arterial pressures occur in **ramipril**-treated patients. GFR is stable at this stage of the evolution of **diabetic** nephropathy and is unaffected by **ramipril treatment** for 2 yr.

IT **87333-19-5, Ramipril**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(low-dose **ramipril** reduces microalbuminuria in type 1 **diabetic** humans without hypertension)

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 31 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:765779 HCAPLUS
DOCUMENT NUMBER: 134:335855
TITLE: Role of **angiotensin-converting-enzyme** inhibition in patients with renal disease
AUTHOR(S): Manley, Harold J.
CORPORATE SOURCE: Medical School, University of Missouri-Kansas City, Kansas City, MO, 64108, USA
SOURCE: American Journal of Health-System Pharmacy (**2000**), 57(Suppl. 1), S12-S18
CODEN: AHSPEK; ISSN: 1079-2082
PUBLISHER: American Society of Health-System Pharmacists
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 23 refs. Clin. studies evaluating the benefits of **angiotensin-converting-enzyme** (**ACE**) inhibitor **therapy** in patients likely to develop renal disease are reviewed. Patients with **diabetes** or hypertension are at increased risk for development of renal disease. In patients with **diabetic** nephropathy, captopril **therapy** was associated with a 50% reduction in the risk of death, dialysis, and transplantation and a significantly smaller increase in serum creatinine compared with placebo. **Therapy** with enalapril or lisinopril has been shown to limit the progression of renal disease in normoalbuminuric patients with **diabetes**. Long-term **therapy** with enalapril (up to seven years) has demonstrated the ability to preserve renal function in patients with **diabetes** and microalbuminuria. Over 4.5 yr, patients with **diabetes** and at least one other cardiovascular risk factor had significant redns. in the risk of overt nephropathy with **ramipril therapy** compared with placebo. In addition, **ramipril** is associated with preservation of renal function in patients with **nondiabetic** nephropathy. Evidence suggesting a dissociation of the renal hemodynamic and antiproteinuric effects of **ACE** inhibition is presented. These pos. effects of **ACE** inhibition cannot be explained by redns. in blood pressure alone. **ACE** inhibitors

have renoprotective properties beyond systemic blood pressure reduction
REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 32 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:765777 HCAPLUS
DOCUMENT NUMBER: 134:335854
TITLE: Role of **angiotensin-converting-enzyme** inhibitors in the treatment of hypertension
AUTHOR(S): Hilleman, Daniel E.
CORPORATE SOURCE: Department of Pharmacy Practice, Creighton University School of Pharmacy and Allied Health Professions, Omaha, NE, 68178, USA
SOURCE: American Journal of Health-System Pharmacy (**2000**), 57(Suppl. 1), S8-S11
CODEN: AHSPEK; ISSN: 1079-2082
PUBLISHER: American Society of Health-System Pharmacists
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 14 refs. **Therapeutic** goals for the **treatment** of hypertension and the ability of various **angiotensin-converting-enzyme** (**ACE**) inhibitors to meet these goals are presented. The 1997 Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and **Treatment** of High Blood Pressure (JNC-VI) does not recommend **ACE** inhibitors for first-line **therapy** in the **treatment** of hypertension; however, these guidelines do identify compelling indications for **ACE** inhibitor **therapy**, including **diabetes** mellitus (type 1) with proteinuria, heart failure, or previous myocardial infarction with systolic dysfunction. Since the JNC-VI guidelines were developed, the results of a prospective randomized clin. trial in patients with uncomplicated hypertension have demonstrated that **ACE** inhibitor **therapy** is as effective as conventional **treatment** in the prevention of cardiovascular morbidity and mortality. In hypertensive patients with **diabetes**, **therapy** with captopril, enalapril, fosinopril, or **ramipril** has resulted in significant redns. in cardiovascular events. In addition, tight blood pressure control with an **ACE** inhibitor has resulted in a greater reduction in the risk of macrovascular and microvascular complications of **diabetes** than was seen with less tight control. Recent study results support broader use of **ACE** inhibitors for hypertension than was recommended in the JNC-VI guidelines.
REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 33 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:553418 HCAPLUS
DOCUMENT NUMBER: 133:144931
TITLE: Use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors for the manufacture of a medicament for the treatment of diabetic neuropathy
INVENTOR(S): Cameron, Norman Eugene; Cotter, Mary Anne
PATENT ASSIGNEE(S): Astrazeneca UK Limited, UK; University Court of the University of Aberdeen
SOURCE: PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000045818	A1	20000810	WO 2000-GB280	20000201 <--
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2368186	AA	20000810	CA 2000-2368186	20000201 <--
BR 2000007996	A	20011030	BR 2000-7996	20000201 <--
EP 1150678	A1	20011107	EP 2000-901744	20000201 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
TR 200102229	T2	20011221	TR 2001-200102229	20000201 <--
EE 200100405	A	20021015	EE 2001-405	20000201 <--
JP 2002536332	T2	20021029	JP 2000-596938	20000201
NZ 513061	A	20030630	NZ 2000-513061	20000201
AU 763970	B2	20030807	AU 2000-23047	20000201
RU 2239456	C2	20041110	RU 2001-124665	20000201
NZ 525419	A	20041224	NZ 2000-525419	20000201
US 6894058	B1	20050517	US 2001-889409	20000201
ZA 2001005885	A	20021017	ZA 2001-5885	20010717 <--
NO 2001003812	A	20011002	NO 2001-3812	20010803 <--
PRIORITY APPLN. INFO.:			GB 1999-2591 A	19990206
			GB 1999-2594 A	19990206
			WO 2000-GB280 W	20000201

AB The invention relates to a new use of a statin drug in the improvement of diabetic neuropathy, specifically in improving nerve conduction velocity and nerve blood flow in patients suffering diabetes, in particular to pharmaceutical combinations of the statin drug and other agents known to improve diabetic neuropathy such as an aldose reductase inhibitor, an **angiotensin converting enzyme** inhibitor, or an angiotensin II antagonist, which combinations are useful in the prevention and treatment of the complications of diabetes.

IT **87333-19-5, Ramipril**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(HMG-CoA reductase inhibitors for **treatment** of **diabetic** neuropathy, and combinations with other agents)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 34 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:460274 HCAPLUS
DOCUMENT NUMBER: 133:68639
TITLE: Chronic proteinuric nephropathies: outcomes and response to treatment in a prospective cohort of 352 patients with different patterns of renal injury
AUTHOR(S): Ruggenenti, Piero; Perna, Annalisa; Gherardi, Giulia; Benini, Roberto; Remuzzi, Giuseppe
CORPORATE SOURCE: Clinical Research Center for Rare Diseases Aldo e Cele Dacco, Mario Negri Institute for Pharmacological Research, Bergamo, 24125, Italy

SOURCE: American Journal of Kidney Diseases (2000), 35(6), 1155-1165
CODEN: AJKDDP; ISSN: 0272-6386
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The **Ramipril** Efficacy in Nephropathy (REIN) study found that **angiotensin-converting enzyme (ACE)** inhibitors effectively decreased proteinuria, glomerular filtration rate (GFR) decline (ΔGFR), and incidence of end-stage renal disease (ESRD) in patients with proteinuric chronic nephropathies. In this study, we prospectively investigated the main clin. determinants of progression and response to **treatment** in the 352 patients enrolled into the REIN study. Mean ΔGFR (0.56±0.05 [SEM] vs. 0.21±0.05 mL/min/1.73 m2/mo; P = 0.0001) and incidence of ESRD (30% and 10%; P = 0.0001) were more than twice that in patients with proteinuria of 2 g/24 h or greater of protein compared with those with protein less than 2 g/24 h (relative risk [RR], 4.07; 95% confidence interval [CI], 2.20 to 7.52), as well as in patients with hypertension compared with normotension (mean ΔGFR, 0.48±0.05 vs. 0.22±0.05 mL/min/1.73 m2/mon; P = 0.0006; ESRD, 25% vs. 10%; P = 0.004; RR, 3.18; 95% CI, 1.38 to 7.32). Hypertension at study entry (P = 0.038), greater mean blood pressure on follow-up (P = 0.002), and urinary protein excretion rate (P = 0.0001) were independent predictors of faster ΔGFR. ΔGFR was approx. twofold faster in patients with type 2 **diabetes** than in those with primary glomerular disease (P = 0.002; including IgA [IgA] nephropathy, P = 0.009); nephrosclerosis (P = 0.03), adult polycystic kidney disease (APKD), or chronic interstitial nephritis (P = 0.006). **Diabetes** at study entry (P = 0.02) and greater mean blood pressure (P = 0.0001) and urinary protein excretion rate (P = 0.0001) on follow-up were independent predictors of faster ΔGFR. After correction for baseline covariates, **diabetes** was also associated with an increased risk for progression to ESRD (RR, 2.39; 95% CI, 1.01 to 5.68; P < 0.05). At multivariate analyses, **ramipril** significantly decreased ΔGFR (regression coefficient, -0.23±0.11 [SEM]; P = 0.036) and ESRD (RR, 2.08; 95% CI, 1.21 to 3.57; P = 0.008) in patients with baseline proteinuria of 2 g/24 h or greater of protein, and the renoprotective effect increased for increasing levels of proteinuria. **Ramipril** decreased ΔGFR to a similar extent in normotensive and hypertensive patients (-0.14±0.11 vs. -0.14±0.09) and significantly limited ESRD in hypertensive patients (RR, 2.03; 95% CI, 1.26 to 3.26; P = 0.004). ΔGFR was decreased by 42% in primary glomerular disease (P = 0.017), by 35% in IgA nephropathy, and by 37% in nephrosclerosis, but was not improved in type 2 **diabetes**, APKD, or interstitial nephritis. At multivariate analyses, **ramipril** significantly slowed ΔGFR (-0.24±0.08; P = 0.004) and progression to ESRD (RR, 2.32; 95% CI, 1.36 to 3.96; P = 0.002) in patients without **diabetes**, but not in patients with **diabetes**, who tended to have a faster ΔGFR (+0.62±0.44) on **ramipril therapy.** In summary, patients with proteinuria of 2 g/24 h or greater of protein, preexisting hypertension, or type 2 **diabetes** were faster progressors. Greater blood pressure and degree of proteinuria were the strongest determinants of faster GFR decline. The renoprotective effect of **ramipril** was similar in patients with normotension and hypertension. Hypertensive patients and those with proteinuria of 2 g/24 h or greater of protein, primary glomerular disease, or nephrosclerosis gained the most from **ACE** inhibitor **treatment.** During the study period, those with proteinuria less than 2 g/24 h of protein, type 2 **diabetes**, or polycystic kidney disease did not benefit by **treatment** to an appreciable extent.

IT **87333-19-5, Ramipril**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(outcomes and response to **ramipril treatment** in human chronic proteinuric nephropathies with different patterns of renal injury)
REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 35 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:415120 HCAPLUS
DOCUMENT NUMBER: 133:12194
TITLE: Ramipril
AUTHOR(S): Smith, W. H. T.; Ball, S. G.
CORPORATE SOURCE: Institute for Cardiovascular Research, University of Leeds, Leeds, LS2 9JT, UK
SOURCE: International Journal of Clinical Practice (**2000**), 54(4), 255-260
CODEN: IJCPF9; ISSN: 1368-5031
PUBLISHER: Medicom International
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 35 refs. **Ramipril** is a long-acting, lipophilic **angiotensin converting enzyme** inhibitor, its principle action is to inhibit the conversion of angiotensin I to the active angiotensin II. **Ramipril** is indicated in the **treatment** of hypertension, congestive cardiac failure (including that following acute myocardial infarction), nephropathy (with and without **diabetes** mellitus) and now, following the findings of the HOPE study, in the prevention of cardiovascular events (including myocardial infarction) in high risk individuals. This article concs. on reviewing the evidence supporting **ramipril**'s use in these indications.
IT **87333-19-5, Ramipril**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effect of **ramipril** for **treatment** of hypertension)
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 36 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:297701 HCAPLUS
DOCUMENT NUMBER: 133:202813
TITLE: **ACE** genotype and **ACE** inhibitors induced renoprotection in chronic proteinuric nephropathies
AUTHOR(S): Perna, Annalisa; Ruggenenti, Piero; Testa, Alessandra; Spoto, Belinda; Benini, Roberto; Misefari, Valerio; Remuzzi, Giuseppe; Zoccali, Carmine; Remuzzi, G.; Tognoni, G.; Ruggenenti, P.; Pisoni, R.; Mosconi, L.; Bertani, T.; Mazzi, A.; Garini, G.; Borghetti, A.; Oliva, E.; Zoccali, C.; Piperno, R.; Rosati, A.; Salvadori, M.; Toti, G.; Sisca, S.; Maggiore, Q.; Dissegna, D.; Brendolan, A.; Greca, G. La; Scanferla, F.; Bazzato, G.; Landini, S.; Pignone, E.; Boero, R.; Piccoli, G.; Quarello, F.; Giannico, G.; Vitale, O.; Manno, C.; Schena, F. P.; Cofano, F.; Fellin, G.; D'Amico, G.; Gandini, E.; D'Amato, I.; Giangrande, A.; Garneri, G.; Giacchino, F.; Feriozzi, A.; Ancarani,

E.; Bossini, N.; Viola, B. F.; Scolari, F.; Maiorca, R.; Perna, A.; Benini, R.; Tammuzzo, L.; Gaspari, F.; Arnoldi, F.; Signorini, O.; Ferrari, S.; Guerini, E.; Migone, L.; Marubini, E.; Del Favero, A.; Ideo, G.; Geraci, E.; Loi, U.

CORPORATE SOURCE: Clinical Research Center for Rare Diseases, Mario Negri Institute for Pharmacological Research, Bergamo, Italy

SOURCE: Kidney International (**2000**), 57(1), 274-281
CODEN: KDYIA5; ISSN: 0085-2538

PUBLISHER: Blackwell Science, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Background. Whether **angiotensin-converting enzyme** (**ACE**) gene polymorphism affects disease progression and response to **ACE** inhibitor **therapy** in **nondiabetic** proteinuric nephropathies is not clearly established. Methods. The relationship between insertion/deletion (I/D) genotypes and proteinuria, rate of glomerular filtration rate decline (ΔGFR)-centrally evaluated by repeated measures of iohexol plasma clearance-and incidence of end-stage renal disease (ESRD) was prospectively evaluated in 212 patients with **nondiabetic** proteinuric chronic nephropathies enrolled in the **Ramipril** Efficacy in Nephropathy (REIN) trial, where patients were randomly assigned to **ramipril** or conventional **treatment.** Results. The ΔGFR ± SEM (-0.38 ± 0.09 vs. -0.50 ± 0.08 vs. -0.36 ± 0.06 mL/min/1.73 m2 per mo) and incidence of ESRD (19 vs. 22 vs. 25%) in the three subgroups with the II, ID, and DD genotypes, resp., were comparable. Of note, ΔGFR (-0.28 ± 0.07 vs. -0.43 ± 0.09 mL/min/1.73 m2 per mo) and incidence of ESRD [14% vs. 36%, P = 0.04, RR (95% CI), 2.62 (1.02 to 6.71)] were lower in **ramipril** than in conventionally treated patients in the DD genotype, but not in the II and ID genotype. Either at univariate (P = 0.04) or at multivariate (P = 0.01) anal., **ramipril** significantly predicted a lower incidence of events in DD, but not in II and ID patients. At three months, **ramipril** decreased proteinuria more effectively in DD (-38.2%) than in the II (-26.7%) or ID (-19.2%) genotype. In DD (but not in II or ID) **ramipril**-treated patients, a short-term reduction in proteinuria correlated with ΔGFR over the entire follow-up period (P = 0.02, r = -0.41). Conclusions. In **nondiabetic** proteinuric nephropathies, the **ACE** I/D polymorphism does not predict disease progression, but is a strong predictor of **ACE** inhibition-associated renoprotection in that proteinuria, ΔGFR, and progression to ESRD are effectively reduced in patients with the DD, but not in those with the II or ID genotype.

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 37 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2000:192931 HCAPLUS

DOCUMENT NUMBER: 132:288613

TITLE: The effect of urapidil and **ramipril** on hyperglycemia in streptozotocin **diabetic** rats

AUTHOR(S): Ittner, Karl Peter; Zimmermann, Markus; Bucher, Michael; Gessele, Wolfgang; Kees, Frieder; Kramer, Bernhard K.; Grobecker, Horst F.

CORPORATE SOURCE: Department of Pharmacology, University of Regensburg, Regensburg, 93040, Germany

SOURCE: Naunyn-Schmiedeberg's Archives of Pharmacology (

2000), 361(1), 92-97
CODEN: NSAPCC; ISSN: 0028-1298
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Angiotensin-converting enzyme** inhibitors and α1-adrenoceptor antagonists improve glucose disposal in **diabetes** mellitus. We compared the effect of the antihypertensive hybrid **drug** urapidil [α1-adrenoceptor antagonist serotonin 1A (5-hydroxytryptamine 1A, 5-HT1A) receptor agonist] on hyperglycemia in streptozotocin **diabetic** rats with the **angiotensin-converting enzyme** inhibitor **ramipril.** 5-HT1A receptor agonists induce hyperglycemia. This could be an important disadvantage during **treatment** of **diabetes** mellitus with urapidil. **Diabetes** was induced by streptozotocin (70 mg/kg i.p.). **Treatment** for 7 days (**ramipril** 10 mg/kg p.o.; urapidil 20 mg/kg p.o.) significantly decreased mean **blood glucose** values (urapidil: 15.7±0.9 mmol/l, P=0.007; **ramipril**: 15.0±0.8 mmol/l, P=0.038 vs. **diabetic** control group: 18.7±1.0 mmol/l). Both **drugs** reduced significantly **blood** pressure, urinary **glucose**, water consumption, and food requirement. Serotonin concentration in the brain (medulla oblongata, pituitary) was not affected. A normalization comparable with healthy control rats was observed only in a **diabetic** control group with insulin **therapy.** In conclusion, our results demonstrate that the antihypertensive **drug** urapidil has no detrimental effect on hyperglycemia compared with the **angiotensin-converting enzyme** inhibitor **ramipril** in exptl. **diabetes** mellitus despite its 5-HT1A receptor agonistic properties.
IT **87333-19-5, Ramipril**
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antihypertensive **drug** urapidil has no detrimental effect on **diabetic** hyperglycemia compared with **ramipril** despite its 5-HT1A receptor agonistic properties)
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 38 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:134336 HCAPLUS
DOCUMENT NUMBER: 132:132099
TITLE: Effects of **ramipril** on cardiovascular and microvascular outcomes in people with **diabetes** mellitus: results of the HOPE study and MICRO-HOPE substudy
AUTHOR(S): Gerstein, Hertzel C.
CORPORATE SOURCE: Canadian Cardiovascular Collaboration Project Office, HGH-McMaster Clinic, Hamilton, ON, L8L 2X2, Can.
SOURCE: Lancet (**2000**), 355(9200), 253-259
CODEN: LANCAO; ISSN: 0140-6736
PUBLISHER: Lancet Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Diabetes** mellitus is a strong risk factor for cardiovascular and renal disease. We investigated whether the **angiotensin-converting-enzyme** (**ACE**) inhibitor **ramipril** can lower these risks in patients with **diabetes**. 3577 People with **diabetes** included in the Heart Outcomes

Prevention Evaluation study, aged 55 yr or older, who had a previous cardiovascular event or at least one other cardiovascular risk factor, no clin. proteinuria, heart failure, or low ejection fraction, and who were not taking **ACE** inhibitors, were randomly assigned **ramipril** (10 mg/day) or placebo, and vitamin E or placebo, according to a two-by-two factorial design. The combined primary outcome was myocardial infarction, stroke, or cardiovascular death. Overt nephropathy was a main outcome in a substudy. The study was stopped 6 mo early (after 4·5 yr) by the independent data safety and monitoring board because of a consistent benefit of **ramipril** compared with placebo. **Ramipril** lowered the risk of the combined primary outcome by 25% (95% Cl 12-36, p=0·0004), myocardial infarction by 22% (6-36), stroke by 33% (10-50), cardiovascular death by 37% (21-51), total mortality by 24% (8-37), revascularization by 17% (2-30), and overt nephropathy by 24% (3-40, p=0·027). After adjustment for the changes in systolic (2·4 mm Hg) and diastolic (1·0 mm Hg) blood pressures, **ramipril** still lowered the risk of the combined primary outcome by 25% (12-36, p=0·0004). **Ramipril** was beneficial for cardiovascular events and overt nephropathy in people with **diabetes.** The cardiovascular benefit was greater than that attributable to the decrease in blood pressure. This **treatment** represents a vasculoprotective and renoprotective effect for people with **diabetes.**

IT **87333-19-5, Ramipril**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of **ramipril** on cardiovascular and microvascular outcomes in humans with **diabetes** mellitus)

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 39 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:86759 HCAPLUS
DOCUMENT NUMBER: 132:121879
TITLE: Vitamin E supplementation and cardiovascular events in high-risk patients
CORPORATE SOURCE: The Heart Outcomes Prevention Evaluation Study Investigators, USA
SOURCE: New England Journal of Medicine (**2000**), 342(3), 154-160
CODEN: NEJMAG; ISSN: 0028-4793
PUBLISHER: Massachusetts Medical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Observational and exptl. studies suggest that the amount of vitamin E ingested in food and in supplements is associated with a lower risk of coronary heart disease and atherosclerosis. We enrolled a total of 2545 women and 6996 men 55 yr of age or older who were at high risk for cardiovascular events because they had cardiovascular disease or **diabetes** in addition to one other risk factor. These patients were randomly assigned according to a two-by-two factorial design to receive either 400 IU of vitamin E daily from natural sources or matching placebo and either an **angiotensin-converting-enzyme** inhibitor (**ramipril**) or matching placebo for a mean of 4.5 yr (the results of the comparison of **ramipril** and placebo are reported in a companion article). The primary outcome was a composite of myocardial infarction, stroke, and death from cardiovascular causes. The secondary outcomes included unstable angina, congestive heart failure, revascularization or amputation, death from any cause, complications of

diabetes, and cancer. A total of 772 of the 4761 patients assigned to vitamin E (16.2 %) and 739 of the 4780 assigned to placebo (15.5 %) had a primary outcome event (relative risk, 1.05; 95 % confidence interval, 0.95 to 1.16; P=0.33). There were no significant differences in the nos. of deaths from cardiovascular causes (342 of those assigned to vitamin E vs. 328 of those assigned to placebo; relative risk, 1.05; 95 % confidence interval, 0.90 to 1.22), myocardial infarction (532 vs. 524; relative risk, 1.02; 95 % confidence interval, 0.90 to 1.15), or stroke (209 vs. 180; relative risk, 1.17; 95 % confidence interval, 0.95 to 1.42). There were also no significant differences in the incidence of secondary cardiovascular outcomes or in death from any cause. There were no significant adverse effects of vitamin E. In patients at high risk for cardiovascular events, **treatment** with vitamin E for a mean of 4.5 yr has no apparent effect on cardiovascular outcomes.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 40 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:86758 HCAPLUS
DOCUMENT NUMBER: 132:117366
TITLE: Effects of an **angiotensin-converting -enzyme** inhibitor, ramipril, on cardiovascular events in high-risk patients
CORPORATE SOURCE: The Heart Outcomes Prevention Evaluation Study Investigators, USA
SOURCE: New England Journal of Medicine (**2000**), 342(3), 145-153
CODEN: NEJMAG; ISSN: 0028-4793
PUBLISHER: Massachusetts Medical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Angiotensin-converting-enzyme** inhibitors improve the outcome among patients with left ventricular dysfunction, whether or not they have heart failure. We assessed the role of an **angiotensin-converting-enzyme** inhibitor, **ramipril**, in patients who were at high risk for cardiovascular events but who did not have left ventricular dysfunction or heart failure. A total of 9297 high-risk patients (55 yr of age or older) who had evidence of vascular disease or **diabetes** plus one other cardiovascular risk factor and who were not known to have a low ejection fraction or heart failure were randomly assigned to receive **ramipril** (10 mg once per day orally) or matching placebo for a mean of five years. The primary outcome was a composite of myocardial infarction, stroke, or death from cardiovascular causes. The trial was a two-by-two factorial study evaluating both **ramipril** and vitamin E. The effects of vitamin E are reported in a companion paper. A total of 651 patients who were assigned to receive **ramipril** (14.0 %) reached the primary end point, as compared with 826 patients who were assigned to receive placebo (17.8 %) (relative risk, 0.78; 95 % confidence interval, 0.70 to 0.86; P<0.001). **Treatment** with **ramipril** reduced the rates of death from cardiovascular causes (6.1 %, as compared with 8.1 % in the placebo group; relative risk, 0.74; P<0.001), myocardial infarction (9.9 % vs. 12.3 %; relative risk, 0.80; P<0.001), stroke (3.4 % vs. 4.9 %; relative risk, 0.68; P<0.001), death from any cause (10.4 % vs. 12.2 %; relative risk, 0.84; P=0.005), revascularization procedures (16.0 % vs. 18.3 %; relative risk, 0.85; P=0.002), cardiac arrest (0.8 % vs. 1.3 %; relative risk, 0.63; P=0.03), heart failure (9.0 % vs. 11.5 %; relative risk, 0.77; P<0.001), and complications related to **diabetes** (6.4 % vs. 7.6 %; relative risk, 0.84; P=0.03). **Ramipril** significantly reduces the rates

of death, myocardial infarction, and stroke in a broad range of high-risk patients who are not known to have a low ejection fraction or heart failure.

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 41 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:575018 HCAPLUS
DOCUMENT NUMBER: 131:280854
TITLE: Comparative assessment of **ACE** inhibitors: what differences are relevant?
AUTHOR(S): Fischler, M. P.; Follath, F.
CORPORATE SOURCE: Medizinische Klinik A, Universitatsspital Zurich, Zurich, CH-8091, Switz.
SOURCE: Schweizerische Medizinische Wochenschrift (**1999**), 129(29/30), 1053-1060
CODEN: SMWOAS; ISSN: 0036-7672
PUBLISHER: Schwabe & Co. AG
DOCUMENT TYPE: Journal; General Review
LANGUAGE: German
AB A review with 33 refs. is given. **ACE** inhibitors are well established in the **treatment** of arterial hypertension, heart failure, and **diabetic** and/or hypertensive nephropathy with albuminuria. The important trials for the various indications are briefly discussed. In Switzerland 11 **ACE** inhibitors are available for clin. use, differing mainly in their **pharmacokinetic** and **pharmacodynamic** properties. The characteristics of practical relevance regarding oral bioavailability, elimination mechanisms, and half-life, as well as the necessary dosage modifications in patients with renal, hepatic, and cardiac failure, are presented. All **ACE** inhibitors except captopril and lisinopril are administered as **prodrugs.** The bioavailability among **ACE** inhibitors varies widely with a range from 11% (trandolapril) to >60% (captopril). The great majority of **ACE** inhibitors are eliminated predominantly through the kidneys. However, benazepril, fosinopril, **ramipril**, spirapril, and trandolapril also have a hepatic (metabolic) route of elimination. Since half-life varies from 1 h (captopril) to 30 h (spirapril) we drew up, for simplicity, a table of 3 groups with short, medium, and long t1/2. In renal insufficiency dose adjustment is required only below a creatinine-clearance level of 30 mL/min. These dosage redns. are not required in liver diseases, but renally excreted **drugs** such as lisinopril should be preferred. **Treatment** with **ACE** inhibitors in severe heart failure should be initiated carefully, with low doses and concomitant diuretic **treatment** added or maintained. Most common adverse effects of **ACE** inhibitors are hypotension, cough, hyperkalemia, and renal failure. Less frequent adverse effects are angioedema, bone marrow suppression, and also fetal damage. Thus, **ACE** inhibitors are contraindicated in pregnancy.
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 42 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:522081 HCAPLUS
DOCUMENT NUMBER: 131:165141
TITLE: Renoprotective properties of **ACE**-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria
AUTHOR(S): Ruggenenti, Piero; Perna, Annalisa; Gherardi, Giulia; Garini, Giovanni; Zoccali, Carmine; Salvadori,

Maurizio; Scolari, Francesco; Schena, Francesco Paolo; Remuzzi, Giuseppe
CORPORATE SOURCE: Institute for Pharmacological Research, Clinical Research Centre for Rare Diseases "Aldo e Cele Dacco" Villa, Bergamo, 24125, Italy
SOURCE: Lancet (**1999**), 354(9176), 359-364
CODEN: LANCAO; ISSN: 0140-6736
PUBLISHER: Lancet Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Background Stratum 2 of the **Ramipril** Efficacy in Nephropathy (REIN) study has already shown that in patients with chronic nephropathies and proteinuria of 3 g or more per 24 h, **angiotensin-converting enzyme** (**ACE**) inhibition reduced the rate of decline in glomerular filtration and halved the combined risk of doubling of serum creatinine or end-stage renal failure (ESRF) found in controls on placebo plus conventional antihypertensives. In REIN stratum 1, reported here, 24 h proteinuria was 1 g or more but less than 3 g per 24 h. Methods In stratum 1 of this double-blind trial 186 patients were randomized to a **ramipril** or a control (placebo plus conventional antihypertensive **therapy**) group targeted at achieving a diastolic blood pressure of less than 90 mm Hg. The primary endpoints were change in glomerular filtration rate (GFR) and time to ESRF or overt proteinuria (≥3 g/24 h). Median follow-up was 31 mo. Findings The decline in GFR per mo was not significantly different (**ramipril** 0.26 [SE 0.05] mL per min per 1.73m2, control 0.29 [0.06]). Progression to ESRF was significantly less common in the **ramipril** group (9/99 vs. 18/87) for a relative risk (RR) of 2.72 (95% Cl 1.22-6.08); so was progression to overt proteinuria (15/99 vs. 27/87, RR 2.40 [1.27-4.52]). Patients with a baseline GFR of 45 mL/min/1.73 m2 or less and proteinuria of 1.5 g/24 h or more had more rapid progression and gained the most from **ramipril treatment.** Proteinuria decreased by 13% in the **ramipril** group and increased by 15% in the controls. Cardiovascular events were similar. As expected, the rate of decline in GFR and the frequency of ESRF were much lower in stratum 1 than they had been in stratum 2. Interpretation In non-**diabetic** nephropathies, **ACE** inhibition confers renoprotection even to patients with non-nephrotic proteinuria.
IT **87333-19-5**, **Ramipril**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**ACE**-inhibitor, **ramipril** effect in non-**diabetic** nephropathies with non-nephrotic proteinuria in humans)
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 43 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:200515 HCAPLUS
DOCUMENT NUMBER: 130:332572
TITLE: Response of serum total renin to ramipril and metoprolol in hypertensive patients
AUTHOR(S): Matinlauri, I. H.; Vesalainen, R. K.; Gronroos, P. E.; Aalto, M.; Kantola, I. M.; Irjala, K. M.
CORPORATE SOURCE: Department of Clinical Chemistry, Turku University Central Hospital, Turku, Finland
SOURCE: Scandinavian Journal of Clinical and Laboratory Investigation (**1998**), 58(8), 655-660
CODEN: SJCLAY; ISSN: 0036-5513

PUBLISHER: Scandinavian University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Renin-angiotensin system has long been thought to be a classic endocrine neg. feedback system in the pathophysiol. of hypertension. Furthermore, angiotensin II formation was believed to be regulated by renin secreted from the kidneys. In contrast to these considerations is the identification of local angiotensin II production in other tissues than pulmonary vasculature. Prorenin, the mol. precursor of renin, has been assumed to be involved in local angiotensin II production because of its renin-like activity. Prorenin has also been found to be secreted from extrarenal sources, although a major part of it is derived from the kidneys. Increased concentration of total renin in serum has been proposed to be useful in identifying patients with active proliferative retinopathy in insulin-dependent **diabetic** patients. Renin-angiotensin system is strongly affected by **angiotensin-converting enzyme** (**ACE**) inhibitors and therefore the interfering effect of **ACE** inhibitor **medication** on total renin concentration should be known in order to interpret serum total renin concns. Nine hypertensive outpatients, all men, treated at the department of internal **medicine** in Turku University Central Hospital, received randomly 5 mg of **ramipril** or 95 mg of metoprolol once a day for 4 wk. **Ramipril** significantly increased the mean value of total renin (191.9 ng/l vs 312.0 ng/l, $p<0.01$), but the metoprolol-induced increase in the concentration of serum total renin was insignificant. We conclude that the neg. feedback mechanism in regulating renin and prorenin secretion was inhibited by **ACE** inhibitor **ramipril** but beta1-selective adrenoceptor antagonist metoprolol did not significantly change total renin concentration in serum.
REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 44 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:64711 HCAPLUS
DOCUMENT NUMBER: 130:129982
TITLE: Pharmaceutical compositions comprising an aldose reductase inhibitor and an **ACE** inhibitor
INVENTOR(S): Carey, Frank; Tuffin, David Patrick; Cameron, Norman Eugene; Cotter, Mary Anne
PATENT ASSIGNEE(S): Zeneca Limited, UK
SOURCE: PCT Int. Appl., 14 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9902189	A1	19990121	WO 1998-GB1959	19980702 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2292451	AA	19990121	CA 1998-2292451	19980702 <--

AU 9882296	A1	19990208	AU 1998-82296	19980702 <--
AU 746211	B2	20020418		
EP 991424	A1	20000412	EP 1998-932358	19980702 <--
EP 991424	B1	20010912		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI				
TR 9903026	T2	20000421	TR 1999-9903026	19980702 <--
BR 9810570	A	20000919	BR 1998-10570	19980702 <--
NZ 501165	A	20010629	NZ 1998-501165	19980702 <--
AT 205402	E	20010915	AT 1998-932358	19980702 <--
ES 2163283	T3	20020116	ES 1998-932358	19980702 <--
PT 991424	T	20020228	PT 1998-932358	19980702 <--
JP 2002509540	T2	20020326	JP 1999-508310	19980702 <--
CZ 290276	B6	20020612	CZ 2000-17	19980702 <--
RU 2216354	C2	20031120	RU 2000-102888	19980702
ZA 9805993	A	19990118	ZA 1998-5993	19980707 <--
MX 200000103	A	20000831	MX 2000-103	20000103 <--
NO 2000000045	A	20000106	NO 2000-45	20000106 <--
US 6337327	B1	20020108	US 2000-462353	20000107 <--
HK 1028876	A1	20020510	HK 2000-106011	20000922 <--
PRIORITY APPLN. INFO.:			GB 1997-14274 A	19970708
			WO 1998-GB1959 W	19980702

AB The invention relates to pharmaceutical compns. comprising an aldose reductase inhibitor and an **ACE** inhibitor, and their use in the treatment of diabetic complications such as diabetic neuropathy, diabetic retinopathy and diabetic nephropathy. A patient requiring treatment for diabetic neuropathy was treated with ZD 5522 70 mg and lisinopril 10 mg twice daily. Tablets and capsules containing the active ingredients are also provided.

IT **87333-19-5, Ramipril**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aldose reductase inhibitor and **ACE** inhibitor combinations for **treatment** of **diabetic** complications)

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 45 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:20107 HCAPLUS
DOCUMENT NUMBER: 130:246624
TITLE: Felodipine inhibits free-radical production by cytokines and glucose in human smooth muscle cells
AUTHOR(S): Hishikawa, Keiichi; Luscher, Thomas F.
CORPORATE SOURCE: Cardiology Division and Institute of Clinical Pharmacology, University Hospitals, Zurich, CH-8091, Switz.
SOURCE: Hypertension (**1998**), 32(6), 1011-1015
CODEN: HPRTDN; ISSN: 0194-911X
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB An imbalance between nitric oxide (NO) and superoxide is importantly involved in the pathogenesis of vascular disease. Inflammatory stimuli and risk factors contribute to these alterations. Calcium antagonists and **angiotensin-converting enzyme** inhibitors are commonly used cardiovascular **drugs.** To clarify the effect of felodipine and **ramiprilat** on the balance of these free radicals, we stimulated human aortic smooth muscle cells (HASCs) with cytokines (human interleukin-1β, tumor necrosis factor-α,

lipopolysaccharide, and/or interferon-γ) or high glucose in the presence and absence of these compds. Felodipine, but not **ramiprilat**, concentration-dependently inhibited cytokine-induced NO production and NO synthase (NOS) mRNA induction. The antioxidant N-acetylcysteine also inhibited cytokine-induced NO production and induction of inducible NOS mRNA. Moreover, felodipine inhibited cytokine-induced superoxide production both in the presence and absence of an NOS inhibitor, suggesting that it acted as a superoxide scavenger and not as an inhibitor of inducible NOS induction. High glucose **treatment** (22 mmol/L for 48 h) also significantly increased superoxide production in HASCs, and this increase was inhibited in a concentration-dependent manner by felodipine but not by **ramiprilat.** These results suggest that felodipine may exert vascular protective effects by suppressing free radical generation in human smooth muscle cells during activation of inflammatory mechanisms and **diabetic** conditions.

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 46 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1999:6597 HCAPLUS

DOCUMENT NUMBER: 130:232278

TITLE: **Angiotensin converting enzyme** inhibition reduces the expression of transforming growth factor-β1 and type IV collagen in diabetic vasculopathy

AUTHOR(S): Rumble, Jonathan R.; Gilbert, Richard E.; Cox, Alison; Wu, Leonard; Cooper, Mark E.

CORPORATE SOURCE: Department of Medicine, Austin & Repatriation Medical Centre, University of Melbourne, Heidelberg, VIC 3081, Australia

SOURCE: Journal of Hypertension (**1998**), 16(11), 1603-1609
CODEN: JOHYD3; ISSN: 0263-6352

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The purpose of this study was to assess the role of transforming growth factor (TGF)-β1 in the development of **diabetes**-associated mesenteric vascular hypertrophy and in the antitrophic effect of **angiotensin converting enzyme** inhibitors. Streptozotocin-induced **diabetic** and control Sprague-Dawley rats were randomly allocated to **treatment** with the **angiotensin converting enzyme** inhibitor **ramipril** or to no **treatment** and were killed 1 or 3 wk after the streptozotocin injection. Blood was collected and mesenteric vessels removed. Mesenteric vascular weight was measured and TGF-β1 and α1 (type IV) collagen messenger (m)RNA levels were analyzed by Northern anal. Immunohistochem. analyses for TGF-β1 and type IV collagen were also performed. The **diabetic** rats had increased mesenteric vessel weight at 3 wk but not at 1 wk and a concomitant rise in mesenteric TGF-β1 and in α1 (type IV) collagen mRNA levels. **Ramipril treatment** attenuated mesenteric vessel hypertrophy and prevented the increase in TGF-β1 and α1 (type IV) collagen mRNA levels after 3 wk of **diabetes.** The immunohistochem. anal. revealed that **diabetes** was associated with increased TGF-β1 and type IV collagen protein and extracellular matrix accumulation in mesenteric vessels, and this increase was reduced by **ramipril treatment.** These results support the concept that TGF-β is involved in the changes associated with

diabetic vascular disease, and suggest a mechanism by which **angiotensin converting enzyme** inhibitors exert their antitrophic effects.

IT **87333-19-5, Ramipril**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**ACE** inhibition reduces expression of TGF-β1 and type IV collagen in **diabetic** vasculopathy)

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 47 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:726588 HCAPLUS
DOCUMENT NUMBER: 130:119321
TITLE: Effects of dihydropyridine calcium channel blockers, **angiotensin-converting enzyme** inhibition, and blood pressure control on chronic, nondiabetic nephropathies
AUTHOR(S): Ruggenenti, Piero; Perna, Annalisa; Benini, Roberto; Remuzzi, Giuseppe
CORPORATE SOURCE: Mario Negri Institute for Pharmacological Research, Clinical Research Center for Rare Diseases "Aldo e Cele Dacco," Villa Camozzi - Ranica, Bergamo, 24125, Italy
SOURCE: Journal of the American Society of Nephrology (**1998**), 9(11), 2096-2101
CODEN: JASNEU; ISSN: 1046-6673
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Dihydropyridine-type calcium channel blockers (dihydropyridine CCB) adversely affect renal function in **diabetes.** The effects of dihydropyridine CCB on 24-h urinary protein excretion rate and GFR decline (ΔGFR) were prospectively evaluated in 117 **nondiabetic** patients with chronic, proteinuric nephropathies enrolled in the **Ramipril** Efficacy in Nephropathy study and randomized to **angiotensin-converting enzyme** inhibition (ACEI) or placebo plus conventional antihypertensive **therapy.** Sixty-three percent of patients were treated with dihydropyridine CCB. During follow-up, CCB-treated compared with no CCB patients had higher proteinuria (4.8 g/24 h vs. 4.2 g/24 h) and mean arterial BP (MAP). The difference in proteinuria was significant in the placebo group (5.1 g/24 h vs. 4.3 g/24 h), but not in the ACEI group (4.4 g/24 h vs. 4.1 g/24 h). Of note, CCB-treated patients had significantly less proteinuria in the ACEI group compared with placebo. CCB-treated vs. no CCB patients had a faster ΔGFR in the overall study population and in the placebo group, but not in the **Ramipril** group. Proteinuria was comparable in CCB-treated and no CCB patients for MAP ≤100 mmHg, but was higher in CCB-treated patients for MAP >100 mmHg. Similarly, proteinuria was comparable in the placebo and in the ACEI group for MAP ≤100 mmHg, but was higher in the placebo group for MAP >100 mmHg. In CCB- and placebo-treated patients, a linear correlation (for both groups) was found between proteinuria and MAP values. MAP, proteinuria, and ΔGFR in patients given nifedipine vs. those given other dihydropyridine CCB were comparable. Thus, in **nondiabetic** proteinuric nephropathies, dihydropyridine CCB may have an adverse effect on renal protein handling that depends on the severity of hypertension and is minimized by ACEI **therapy** or tight BP control. **ACE** inhibitors may electively limit proteinuria in patients on dihydropyridine

CCB **treatment** and/or with uncontrolled hypertension.

IT **87333-19-5, Ramipril**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dihydropyridine calcium channel blockers, **angiotensin-converting enzyme** inhibition, and blood pressure control effects on chronic **nondiabetic** nephropathies in humans)

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 48 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:413812 HCAPLUS
DOCUMENT NUMBER: 129:173992
TITLE: **Angiotensin converting enzyme** inhibition and calcium antagonism attenuate streptozotocin-diabetes-associated mesenteric vascular hypertrophy independently of their hypotensive action
AUTHOR(S): Cao, Zemin; Hulthen, U. Lennart; Allen, Terri J.; Cooper, Mark E.
CORPORATE SOURCE: Department of Medicine, University of Melbourne, Austin and Repatriation Medical Centre, Heidelberg West, 3081, Australia
SOURCE: Journal of Hypertension (**1998**), 16(6), 793-799
CODEN: JOHYD3; ISSN: 0263-6352
PUBLISHER: Lippincott-Raven Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To investigate the relative roles of angiotensin II, bradykinin, and calcium-dependent pathways in the genesis of mesenteric vascular hypertrophy in exptl. **diabetes.** Streptozotocin-induced **diabetic** Sprague-Dawley rats were randomly allocated to these **treatments** for 24 wk: no **treatment**; **ramipril** at a hypotensive dose; **ramipril** plus the bradykinin type 2 receptor blocker icatibant; icatibant alone; **ramipril** at a low dose; the angiotensin II type 1 receptor antagonist, valsartan; the dihydropyridine calcium antagonist, lacidipine; and the nondihydropyridine calcium antagonist mibefradil. Systolic blood pressure was serially measured every 4 wk by tail-cuff plethysmog. We assessed the vascular architecture in sections of mesenteric arteries obtained after in-vivo perfusion, which were stained with an antibody to α-smooth muscle actin. Both blood pressure and the mesenteric arterial wall: lumen ratio were reduced by administration of **ramipril**, at the high dose, either alone or in combination with icatibant, and also by valsartan. **Treatment** either with the low dose of **ramipril** or with the calcium antagonists lacidipine and mibefradil was associated with a decrease in the wall: lumen ratio of the mesenteric arteries without influencing blood pressure. These findings demonstrate that blockade both of angiotensin II-dependent and of calcium-dependent pathways attenuates mesenteric vascular hypertrophy in exptl. **diabetes.** Furthermore, the antitrophic effects of these antihypertensive agents may be independent of their hypotensive effects.

IT **87333-19-5, Ramipril**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(angiotensin II, bradykinin, and calcium-dependent pathways in genesis of mesenteric vascular hypertrophy in exptl. **diabetes**)

REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 49 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:345132 HCAPLUS
DOCUMENT NUMBER: 129:373
TITLE: Bioenergetics of liver mitochondria in experimental **diabetes** mellitus after the administration of **ramipril**
AUTHOR(S): Ulicna, O.; Cizova, M.; Kolesar, P.; Volkovova, K.; Cibulova, L.; Carsky, J.; Ondrejka, P.
CORPORATE SOURCE: Pharmacobiochemistry Laboratory, IIIrd Internal Clinic, School Medicine, Bratislava, Slovakia
SOURCE: Bratislavske Lekarske Listy (**1997**), 98(12), 687-694
CODEN: BLLIAX; ISSN: 0006-9248
PUBLISHER: Slovak Academic Press Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: Slovak
AB **Angiotensin-converting enzyme** (**ACE**) inhibitors are **drugs** of choice in the **treatment** of hypertension during **diabetes** mellitus. The effects of **ramipril** on glycated Hb and fructosamine levels in blood and on liver mitochondrial bioenergetics were studied in Wistar rats with insulin-dependent **diabetes** mellitus (IDDM) induced by streptozotocin (45 mg/kg i.v.). The rats were treated with insulin (6 U/kg s.c.) and the **ACE** inhibitor **ramipril** intragastrically (10 mg/kg) daily for 8 wk. Glucose, glycated Hb, fructosamine, cholesterol, and triacylglycerols were determined in the blood and liver. Oxidative phosphorylation in liver mitochondria was measured by polarog. In the IDDM + **ramipril** group, the glycated Hb (6.85%) and fructosamine (1.45 mmol/L) were decreased in comparison with the IDDM control group (glycated Hb 8.8%, fructosamine 2.04 mmol/L). **Ramipril** did not affect the concentration of cholesterol and triacylglycerols in the blood and liver in rats with IDDM. **Ramipril** pos. affected mitochondrial oxidative phosphorylation in rats with IDDM. Rats in the IDDM + **ramipril** group had increased mitochondrial oxygen consumption during ADP-stimulated respiration and the phosphorylation rates with NAD/glutamate substrate compared to the control IDDM group. A similar trend was present with FAD/succinate substrate. Thus, after administration of **ramipril** to rats with IDDM the biochem. parameters improved indicating a compensation of **diabetes** mellitus. The increased respiratory chain capacity and energy production in liver mitochondria of rats with IDDM after the administration of **ramipril** indicates an improvement in the liver metabolic capacity.
IT **87333-19-5**, **Ramipril**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**ramipril** effects on liver mitochondrial bioenergetics in rats with **diabetes** mellitus)

L16 ANSWER 50 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:162979 HCAPLUS
DOCUMENT NUMBER: 128:281389
TITLE: Expression of transforming growth factor-β1 and type IV collagen in the renal tubulointerstitium in experimental diabetes: effects of **ACE** inhibition
AUTHOR(S): Gilbert, Richard E.; Cox, Alison; Wu, Leonard L.; Allen, Terri J.; Hulthen, U. Lennart; Jerums, George;

Cooper, Mark E.
CORPORATE SOURCE: Department of Medicine, Austin and Repatriation Medical Centre, University of Melbourne, Heidelberg, 3084, Australia
SOURCE: Diabetes (**1998**), 47(3), 414-422
CODEN: DIAEAZ; ISSN: 0012-1797
PUBLISHER: American Diabetes Association
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Transforming growth factor-β (TGF-β) and the renin-angiotensin system (RAS) have both been implicated in the pathogenesis of glomerulosclerosis in **diabetic** kidney disease. However, tubulointerstitial pathol. may also be an important determinant of progressive renal dysfunction in **diabetic** nephropathy. In the present study, the authors investigated tubulointerstitial injury, TGF-β1 expression, and the effect of blocking the RAS by inhibition of **ACE**. The authors randomized 36 male SD rats to control and **diabetic** groups. **Diabetes** was induced in 24 rats by administration of streptozotocin; 12 **diabetic** rats were further randomized to receive the **ACE** inhibitor **ramipril** (3 mg/l drinking water). At 6 mo, exptl. **diabetes** was associated with tubulointerstitial damage, a 70% increase in expression of TGF-β1 (vs. control), and a 120% increase in α1 (IV) collagen gene expression (vs. control). In situ hybridization demonstrated a diffuse increase in both TGF-β1 and α1 (IV) collagen mRNA in renal tubules. In addition, intense expression of both transcripts was noted in regions of focal tubular dilatation. Administration of the **ACE** inhibitor **ramipril** prevented tubulointerstitial injury and the overexpression of TGF-β1 and α1 (IV) collagen mRNA. Changes in gene expression were accompanied by parallel changes in immunostaining for TGF-β1 and type IV collagen. The observed beneficial effects of **ramipril** on the tubulointerstitium in exptl. **diabetes** suggest that this mechanism may contribute to the **therapeutic** effect of **ACE** inhibitors in **diabetic** nephropathy.
IT **87333-19-5, Ramipril**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(expression of transforming growth factor-β1 and type IV collagen in renal tubulointerstitium in exptl. **diabetes** and effects of **ACE** inhibition)
REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 51 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:119402 HCAPLUS
DOCUMENT NUMBER: 128:149402
TITLE: Microcirculation in hyperglycemic patients with IDDM without diabetic complications. Effect of low-dose **angiotensin-converting enzyme** inhibition
AUTHOR(S): Haak, Eva; Haak, T.; Kusterer, K.; Reschke, B.; Faust, H.; Usadel, K. H.
CORPORATE SOURCE: Medical Dep. I, Center Internal Medicine, Johann Wolfgang Goethe-Universitaet, Frankfurt/Main, D-60590, Germany
SOURCE: Experimental and Clinical Endocrinology & Diabetes (**1998**), 106(1), 45-50
CODEN: ECEDFQ; ISSN: 0947-7349
PUBLISHER: Johann Ambrosius Barth

DOCUMENT TYPE: Journal
LANGUAGE: English
AB In patients with insulin-dependent **diabetes** mellitus (IDDM) **angiotensin-converting enzyme** inhibitors (ACEI) were demonstrated to have beneficial effects in the secondary prevention of microvascular complications. Patients with IDDM received 1.25 mg of **ramipril** (**Delix**, Hoechst Marion Roussel, Frankfurt) over 4 wk. Using nailfold capillaroscopy the authors determined capillary blood cell velocity (CapiFlow, Lawrenz Electronics, Sulzbach, Germany) before and during post-occlusive hyperemia (200 mmHg for 3 min) as a provocative test. Before and after **treatment** patients were studied during hyperglycemia (**blood glucose** 250-350 mg/dL). **Treatment** with low-dose **ramipril** resulted in a decrease in the time to peak capillary blood cell velocity during post-occlusive hyperemia (17.8 vs 57.4 s) in hyperglycemic patients. This effect was absent in healthy. These data demonstrate that low-dose **therapy** with **ramipril** is able to improve microcirculation in hyperglycemic patients with type 1 **diabetes** mellitus also before microvascular complications are evident.
IT **87333-19-5**, **Ramipril**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**ramipril** effect on microcirculation in hyperglycemic IDDM without **diabetic** complications)

L16 ANSWER 52 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:641513 HCAPLUS
DOCUMENT NUMBER: 127:317589
TITLE: Role of angiotensin II and bradykinin in experimental diabetic nephropathy: functional and structural studies
AUTHOR(S): Allen, Terri J.; Cao, Zemin; Youssef, Sherif; Hulthen, U. Lennart; Cooper, Mark E.
CORPORATE SOURCE: Dep. Med., Univ. Melbourne, Australia
SOURCE: Diabetes (**1997**), 46(10), 1612-1618
CODEN: DIAEAZ; ISSN: 0012-1797
PUBLISHER: American Diabetes Association
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors explored the relative roles of the suppression of angiotensin II and the prevention of bradykinin degradation in mediating the renoprotective effects of **ACE** inhibitors in exptl. **diabetic** nephropathy. Over a 24-wk period, the authors studied male Sprague-Dawley **diabetic** and control rats and Sprague-Dawley **diabetic** rats treated with the **ACE** inhibitor **ramipril**, the angiotensin II-AT1 receptor antagonist valsartan, the bradykinin-B2 receptor antagonist HOE 140 (icatibant), and a combination of **ramipril** and icatibant. Serial measurements of urinary albumin excretion, blood pressure, and glycated Hb were performed monthly. After 6 mo, the animals were killed for the measurement of kidney weight and the assessment of glomerular ultrastructure. Over 24 wk, urinary albumin excretion showed a continuous rise in the untreated **diabetic** rats. Both **ramipril** and valsartan, which were equihypotensive, prevented the increase in urinary albumin excretion over the whole study period. Icatibant **therapy** did not attenuate the antialbuminuric effect of the **ACE** inhibitor, nor did it have any effect as the sole **therapy**. **Diabetes** was associated with increased glomerular basement membrane thickness, glomerular volume, and total mesangial volume Both **ACE** inhibition and angiotensin II

receptor antagonism attenuated the glomerular ultrastructural changes to a similar degree. Icatibant did not attenuate the effects of **ramipril** on glomerular morphol. **ACE** inhibitors and angiotensin II-AT1 receptor blockers appear to confer similar benefits in exptl. **diabetic** nephropathy, and bradykinin-B2 receptor blockers do not influence this effect. These findings suggest that the blockade of angiotensin II is the major pathway responsible for renoprotection afforded by **ACE** inhibition in exptl. **diabetic** nephropathy.

REFERENCE COUNT: 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 53 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:519535 HCAPLUS
DOCUMENT NUMBER: 127:171320
TITLE: Combination therapy in hypertension-associated diabetic renal disease
AUTHOR(S): Mogensen, C. E.; Pedersen, M. Mau; Ebbehoj, E.; Logstrup Poulsen, P.; Schmitz, A.
CORPORATE SOURCE: Kommunehospitalet, Univ. Hospital, Aarhus, Den.
SOURCE: International Journal of Clinical Practice (**1997**), (Suppl. 90), 52-58
CODEN: IJCPF9; ISSN: 1368-5031
PUBLISHER: Medicom International
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Diabetic** nephropathy in insulin dependent **diabetes** mellitus (IDDM) and non-insulin dependent **diabetes** mellitus (NIDDM) patients is a common cause of end-stage renal failure. At present, two aspects appear to be a major importance in the intervention against **diabetic** nephropathy-namely optimization of glycemic control (to near euglycemia) and antihypertensive **therapy.** The pathogenesis behind hypertension in **diabetes** may be multifactorial, particularly in NIDDM patients, but it is well recognized that lowering blood pressure is important in patients with nephropathy. **Treatment** with diuretics and beta-blockers, for example, has been shown to improve survival in patients with **diabetic** nephropathy. Diuretics reduce sodium retention, which is a characteristic feature in **diabetes.** The protective action of beta-blockers is probably mainly related to the reduction of systemic blood pressure; however, a reduction in glomerular hyperperfusion may also be relevant, particularly in early nephropathy. Glomerular hypertension is likely to be a pathogenetic factor in **diabetic** nephropathy. **ACE** inhibitors are newer **drugs**, and they seem relevant in incipient and overt **diabetic** nephropathy, as they can apparently reduce glomerular hypertension. In the present small-scale study, we report on long-term effects of combination **treatment** with **ACE** inhibitors, beta blockers and diuretics in seven patients with early nephropathy. Some deterioration in renal function is to be expected in such patients if no antihypertensive **treatment** is given. The patients were followed for four and a half years after an initial double-blind, crossover study with addition of **ACE** inhibitor. The mean doses in the follow-up period were **ramipril**, 5 mg daily (all patients received this dose), metoprolol, 121 mg (range: 50-200) daily, and bendroflumethiazide, 3.2 mg (range: 2.5-7.5) daily. Between year one and year four and a half, no statistically significant decline in glomerular filtration rate was seen (110 ± 8 (mean ± SE) vs 107 ± 7 mL/min/1.73 m2).

IT **87333-19-5, Ramipril**

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination **therapy** in hypertension-associated **diabetic** renal disease in humans)

L16 ANSWER 54 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:467151 HCAPLUS
DOCUMENT NUMBER: 127:130695
TITLE: Randomized placebo-controlled trial of effect of **ramipril** on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-**diabetic** nephropathy
CORPORATE SOURCE: The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia), UK
SOURCE: Lancet (**1997**), 349(9069), 1857-1863
CODEN: LANCAO; ISSN: 0140-6736
PUBLISHER: Lancet
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In **diabetic** nephropathy, **angiotensin-converting-enzyme** (**ACE**) inhibitors have a greater effect than other antihypertensive **drugs** on proteinuria and the progressive decline in glomerular filtration rate (GFR). Whether this difference applies to progression of **nondiabetic** proteinuric nephropathies is not clear. The **Ramipril** Efficacy In Nephropathy study of chronic **nondiabetic** nephropathies aimed to address whether glomerular protein traffic influences renal-disease progression, and whether an **ACE** inhibitor was superior to conventional **treatment**, with the same blood-pressure control, in reducing proteinuria, limiting GFR decline, and preventing end-stage renal disease. In this prospective double-blind trial, 352 patients were classified according to baseline proteinuria (stratum 1: 1-3 g/24 h; stratum 2: ≥3 g/24 h), and randomly assigned **ramipril** or placebo plus conventional antihypertensive **therapy** targeted at achieving diastolic blood pressure under 90 mm Hg. The primary endpoint was the rate of GFR decline. Anal. was by intention to treat. At the second planned interim anal., the difference in decline in GFR between the **ramipril** and placebo groups in stratum 2 was highly significant ($p=0.001$). The Independent Adjudicating Panel therefore decided to open the randomization code and do the final anal. in this stratum (stratum 1 continued in the trial). Data (at least three GFR measurements including baseline) were available for 56 **ramipril**-assigned patients and 61 placebo-assigned patients. The decline in GFR per mo was significantly lower in the **ramipril** group than the placebo group (0.53 [0.08] vs 0.88 [0.13] mL/min, $p=0.03$). Among the **ramipril**-assigned patients, percentage reduction in proteinuria was inversely correlated with decline in GFR ($p=0.035$) and predicted the reduction in risk of doubling of baseline creatinine or end-stage renal failure (18 **ramipril** vs 40 placebo, $p=0.04$). The risk of progression was still significantly reduced after adjustment for changes in systolic ($p=0.04$) and diastolic ($p=0.04$) blood pressure, but not after adjustment for changes in proteinuria. Blood-pressure control and the overall number of cardiovascular events were similar in the two **treatment** groups. In chronic nephropathies with proteinuria of 3 g or more per 24 h, **ramipril** safely reduces proteinuria and the rate of GFR decline to an extent that seems to exceed the reduction expected for the degree of blood-pressure lowering.
IT **87333-19-5, Ramipril**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(**ramipril** effect on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, **nondiabetic** nephropathy)

L16 ANSWER 55 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:366626 HCAPLUS
DOCUMENT NUMBER: 127:75737
TITLE: Cardiovascular effects of a low-dose combination of ramipril and felodipine in spontaneously hypertensive rats
AUTHOR(S): Mervaala, Eero M. A.; Teravainen, Terttu-Liisa; Malmberg, Lena; Laakso, Juha; Vapaatalo, Heikki; Karppanen, Heikki
CORPORATE SOURCE: Institute Biomedicine, Department Pharmacology Toxicology, University Helsinki, FIN-00014, Finland
SOURCE: British Journal of Pharmacology (**1997**), 121(3), 503-510
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Stockton
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cardiovascular effects of submaximal antihypertensive doses of the **angiotensin converting enzyme** inhibitor, **ramipril** (0.25 mg kg-1 day-1 in the food), and the calcium channel blocker, felodipine (0.4 mg kg-1 day-1 s.c. by osmotic minipump), both alone and in combination, were examined in spontaneously hypertensive rats (SHR) in a four-week study. Both **ramipril** and felodipine as **monotherapy** decreased systolic blood pressure. The antihypertensive effect of the **drug** combination was more than that of **ramipril treatment** alone, but now significantly better than that of felodipine **monotherapy.** **Ramipril** or felodipine **treatments** did not significantly affect the heart rate, either alone or in combination. The beneficial effect of **ramipril monotherapy** on left ventricular hypertrophy was more prominent than that of felodipine. The cardioprotective effect of felodipine was improved when combined to **ramipril.** The systolic blood pressure at the end of the exptl. period correlated only weakly with left ventricular hypertrophy. Responses of mesenteric arterial rings in vitro were examined at the end of the four-week study. **Ramipril** and felodipine **monotherapies** as well as their combination markedly improved the endothelium-dependent vascular relaxation responses to acetylcholine. The combination of **ramipril** and felodipine slightly enhanced the endothelium-independent vascular relaxation responses to sodium nitroprusside. **Ramipril treatment** alone slightly diminished the vascular contractile responses to noradrenaline. Neither **ramipril** nor felodipine alone or in combination affected the vascular contractile responses to potassium chloride. **Ramipril treatment**, both alone and in combination with felodipine, caused a three fold increase in plasma renin activity. Serum aldosterone, fasting **blood glucose** level, serum insulin and the 24 h urinary excretions of sodium, potassium, magnesium, calcium, phosphorus or protein were not significantly affected by the **drug treatments** . Our findings suggest that a better overall control of hypertension and end-organ damages, without an increase in adverse effects, can be achieved by the combination of submaximal antihypertensive doses of felodipine and **ramipril** than by **monotherapy** with either **drug** alone.

L16 ANSWER 56 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1997:353104 HCAPLUS
DOCUMENT NUMBER: 127:79637
TITLE: Cardiac hypertrophy in diabetic spontaneously hypertensive rats: role of angiotensin II?
AUTHOR(S): Black, M. Jane; Briscoe, Todd; Bertram, John F.; Jackson, Bruce; Johnston, Colin I.
CORPORATE SOURCE: Department of Medicine, Austin & Repatriation Medical Centre, The University of Melbourne, Heidelberg, 3084, Australia
SOURCE: Clinical and Experimental Pharmacology and Physiology (**1997**), 24(6), 445-448
CODEN: CEXPB9; ISSN: 0305-1870
PUBLISHER: Blackwell
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In the present study the role of angiotensin II (AngII) in the development of cardiac hypertrophy in **diabetes** combined with hypertension was investigated. **Diabetes** was induced in 8-wk-old male spontaneously hypertensive rats (SHR) by i.v. injection of streptozotocin (45 mg/kg bodyweight). **Diabetic** SHR were treated with the **angiotensin-converting enzyme** (**ACE**) inhibitor **ramipril** at a dose of 0.4 mg/kg per day. Twelve weeks following the onset of **diabetes**, hearts were arrested in diastole and were perfusion-fixed. The right ventricle and left ventricle plus septum were weighted and the volume of the ventricular walls was determined using the Cavalieri principle. Induction of **diabetes** in SHR led to a significant reduction in bodyweight compared with non-**diabetic** control SHR and this was not affected by **ramipril** **treatment.** The development of hypertension was not as great in **diabetic** SHR compared with controls, such that at 12 wk following the onset of **diabetes** systolic blood pressures (SBP) averaged 191±3 and 230±4 mmHg in **diabetic** SHR and controls, resp. **Ramipril treatment** significantly lowered SBP in **diabetic** SHR. The left ventricle plus septum volume:bodyweight ratio (LV vol:BW) was significantly higher in **diabetic** SHR compared with controls (3.83±0.19 and 3.26±0.16 mm3/g, resp.). **Ramipril treatment** did not affect growth of the left ventricle in **diabetic** SHR with the LV vol:BW ratio averaging 3.95±0.14 mm3/g. Similar trends on growth were observed in the right ventricle. In conclusion, the development of cardiac hypertrophy in **diabetic** SHR appears to occur by mechanisms independent of AngII and the elevation of blood pressure.

IT **87333-19-5**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cardiac hypertrophy in **diabetic** spontaneously hypertensive rat occurs by mechanisms independent of angiotensin II as determined by the **ACE** inhibitor **ramipril** and the elevation of blood pressure)

REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 57 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:266821 HCAPLUS
DOCUMENT NUMBER: 126:338639
TITLE: Short-term **treatment** with **ramipril** normalizes renal hemodynamics and the natriuretic response to a sodium load in type 1 **diabetic**

patients with early nephropathy
AUTHOR(S): Stenvinkel, P.; Bolinder, J.; Alvestrand, A.
CORPORATE SOURCE: Karolinska Institute, Huddinge University Hospital, Huddinge, S-14186, Swed.
SOURCE: Acta Diabetologica (**1997**), 34(1), 10-17
CODEN: ACDAEZ; ISSN: 0940-5429
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The influence of acute inhibition of **angiotensin converting enzyme** (**ACE**) on intrarenal Na handling, renal hemodynamics, and renal dopamine output in response to an i.v. NaCl infusion was studied in diabetic patients with elevated urinary albumin excretion. Two days of **ACE** inhibition improved the natriuretic response within the 1st 2 h following an i.v. 2-h NaCl infusion (12.5 mL kg-1 h-1) due to a normalization of the proximal tubular Na handling. Following NaCl infusion, only a blunted increase of urinary dopamine output was seen, which tended to normalize following inhibition of **ACE.**
IT **87333-19-5, Ramipril**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**ramipril** normalized renal hemodynamics and the natriuretic response to a Na load in type 1 **diabetic** early nephropathy)

L16 ANSWER 58 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:23897 HCAPLUS
DOCUMENT NUMBER: 126:84332
TITLE: Effect of **ramipril** on blood pressure and protein excretion rate in normotensive **nondiabetic** patients with proteinuria
AUTHOR(S): Toto, Robert D.; Adams-Huet, Beverley; Fenves, Andrew Z.; Mitchell, Helen C.; Mulcahy, Wayne; Smith, Ronald D.
CORPORATE SOURCE: Southwestern Medical Center, University Texas, Dallas, TX, 75235-8856, USA
SOURCE: American Journal of Kidney Diseases (**1996**), 28(6), 832-840
CODEN: AJKDDP; ISSN: 0272-6386
PUBLISHER: Saunders
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Angiotensin-converting enzyme** inhibitors reduce proteinuria in both normotensive and hypertensive patients with proteinuric renal disease. However, the mechanism of the antiproteinuric effect has not been clarified. The authors performed a prospective, double-blind, placebo-controlled, randomized crossover trial to test the hypothesis that the antiproteinuric effect of **ramipril** was due to an improvement in glomerular permselectivity independent of blood pressure and glomerular filtration rate. The effect of low-dose (1.25 mg/d) and high-dose (5 mg/d) **ramipril** was assessed in 15 normotensive **nondiabetic** patients with proteinuria (> 150 mg/d). The study was divided into four 12-wk periods: placebo, high- or low-dose **ramipril**, crossover to low- or high-dose **ramipril**, and placebo. Blood pressure, glomerular filtration rate, renal plasma flow rate, urinary protein excretion rate, and plasma angiotensin II levels were measured at the end of each period. Mean arterial pressure, urine protein to creatinine ratio, and albumin excretion rate decreased significantly during low- and high-dose **ramipril.** Glomerular filtration rate and renal plasma flow rate were not changed significantly. Plasma angiotensin II levels decreased with both low- and high-dose

ramipril. There were no episodes of hypotension and only one subject developed cough during **ramipril** that did not require discontinuation of the study **drug.** In conclusion, administration of **ramipril** in both low and high doses lowered blood pressure and reduced proteinuria in this cohort of normotensive patients with a variety of proteinuric renal diseases. The antiproteinuric effect of **ramipril** is probably mediated by a reduction in glomerular capillary pressure.

IT **87333-19-5, Ramipril**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effect of **ramipril** on blood pressure and protein excretion rate in normotensive **nondiabetic** human patients with proteinuria)

L16 ANSWER 59 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:4898 HCAPLUS
DOCUMENT NUMBER: 126:87843
TITLE: Interactions of the kallikrein-kinin and renin-angiotensin systems in experimental diabetes
AUTHOR(S): Vora, Jiten P.; Oyama, Terry T.; Thompson, Michele M.; Anderson, Sharon
CORPORATE SOURCE: Div. of Nephrology and Hypertension, Oregon Health Sciences Univ., Portland, OR, 97201-2940, USA
SOURCE: Diabetes (**1997**), 46(1), 107-112
CODEN: DIAEAZ; ISSN: 0012-1797
PUBLISHER: American Diabetes Association, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The kallikrein-kinin system (KKS) has been postulated to play a role in modulation of hemodynamic function in **diabetes** and to contribute to the hemodynamic effects of **angiotensin-converting enzyme** inhibition (CEI). To further explore the KKS and its interactions with the renin-angiotensin system (RAS), studies were conducted in **nondiabetic** control rats and in moderately hyperglycemic **diabetic** rats. In protocol 1, control and **diabetic** rats were studied before and after administration of one of two dissimilar B2 kinin receptor antagonists (BK2As), or vehicle. At a low dose (0.5 μg·kg-1·min-1), the first generation antagonist D-Arg,[Hyp3,Thi5,8,D-Phe7]-bradykinin significantly reduced the glomerular filtration rate (GFR) and renal plasma flow rate in **diabetic** rats, despite variable effectiveness in blocking the hypotensive response to injected bradykinin. However, a similar hemodynamic effect occurred in **nondiabetic** rats, suggesting that the observed effect was not specific to **diabetes.** Higher doses (20 μg bolus, then 1 μg·kg-1·min-1 infusion) did not affect hemodynamics in either group, perhaps because of partial agonist effect. The second BK2A tested was the newer compound, icatibant (Hoe 140; D-Arg,[Hyp3,Thi5,D-Tic7,Oic8]-bradykinin). Hoe 140 consistently blocked the vasodepressor action of injected bradykinin, but had no effect on systemic or renal hemodynamics in either control or **diabetic** rats. In protocol 2, control and **diabetic** rats were prepared with the CEI **ramipril** for 1-2 wk, after which renal function was studied before and after Hoe 140 (0.1 mg s.c. and i.v.) or vehicle. CEI lowered blood pressure in both groups. Hoe 140 did not affect renal function in control rats, but in **diabetic** rats pretreated with **ramipril**, it induced a modest but significant decline in GFR. **Ramipril** induced the predicted changes in the systemic and intrarenal RAS, while acute BK2A had no consistent effect on RAS

parameters. These studies suggest that the endogenous KKS has only a minor role in modulation of renal hemodynamics in the euvolemic **diabetic** rat, in the absence of KKS stimulation by CEI. However, **angiotensin-converting enzyme** is also kininase II, which serves to increase endogenous kinin activity. The increased kinin activity resulting from CEI **treatment** may participate, to a modest degree, in hemodynamic regulation of the **diabetic** kidney.

IT **87333-19-5, Ramipril**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(interactions of kallikrein-kinin and renin-angiotensin systems in exptl. **diabetes** in relation to bradykinin receptor antagonists)

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 60 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:696190 HCAPLUS
DOCUMENT NUMBER: 125:316813
TITLE: Study design and baseline characteristics of the study to evaluate carotid ultrasound changes in patients treated with ramipril and vitamin E: SECURE
AUTHOR(S): Lonn, E. M.; Yusuf, S.; Doris, C. I.; Sabine, M. J.; Dzavik, V.; Hutchison, K.; Riley, W. A.; Tucker, J.; Pogue, J.; et al.
CORPORATE SOURCE: Hamilton Civic Hospitals Research Center, Mc-Master University, Hamilton, ON, Can.
SOURCE: American Journal of Cardiology (**1996**), 78(8), 914-919
CODEN: AJCDAG; ISSN: 0002-9149
PUBLISHER: Excerpta Medica
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Atherosclerotic cardiovascular disease remains a major cause of mortality and morbidity in most developed countries. Exptl. and clin. evidence suggests that **angiotensin-converting enzyme** inhibitors and vitamin E **therapy** may retard the atherosclerotic process; however, definitive proof in humans is lacking. The Study to Evaluate Carotid Ultrasound Changes in Patients Treated with **Ramipril** and Vitamin E (SECURE) is designed to assess the effects of **ramipril**, an **angiotensin-converting enzyme** inhibitor, at 2 doses: 2.5 mg daily (which has little effect on lowering blood pressure) and 10 mg daily and the antioxidant vitamin E, 400 IU daily, on atherosclerosis progression in 732 patients using a factorial 3+2 study design. High-risk patients with a documented history of significant cardiovascular disease or with **diabetes** and addnl. risk factors were enrolled and will be followed for 4 yr. The extent and progression of atherosclerosis are assessed noninvasively by B-mode carotid ultrasonog. The SECURE trial is a sub-study of the larger Heart Outcomes Prevention Evaluation (HOPE) study of 9,541 high-risk patients evaluating the effects of **ramipril** and vitamin E on major cardiovascular events (cardiovascular death, myocardial infarction, and stroke). The 2 studies are complementary. Whereas HOPE is expected to provide information on major clin. outcomes, SECURE will shed light on the mechanisms by which these effects may be mediated.

L16 ANSWER 61 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:619628 HCAPLUS

DOCUMENT NUMBER: 125:265517
TITLE: Vascular hypertrophy and albumin permeability in a rat model combining hypertension and diabetes mellitus. Effects of calcium antagonism, **angiotensin converting enzyme** inhibition, and angiotensin II-AT1-receptor blockade
AUTHOR(S): Hulthen, U. Lennart; Cao, Zemin; Rumble, Jonathan R.; Cooper, Mark E.; Johnston, Colin I.
CORPORATE SOURCE: Austin and Repatriation Medical Centre, University Melbourne, Heidelberg, Australia
SOURCE: American Journal of Hypertension (**1996**), 9(9), 895-901
CODEN: AJHYE6; ISSN: 0895-7061
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The aim of this study was to compare the effects of **angiotensin converting enzyme** (**ACE**) inhibition, angiotensin II (AII) AT1-receptor blockade, and dihydropyridine calcium antagonism on hypertrophy and on vascular albumin permeability in kidney, heart, and mesenteric artery in a model combining genetic hypertension and **diabetes** mellitus. **Diabetes** mellitus was induced by streptozotocin in 8-wk-old spontaneously hypertensive rats. The animals were randomized to receive no **treatment**, the **angiotensin converting enzyme** inhibitor **ramipril**, the AII AT1-receptor blocker valsartan, or the dihydropyridine calcium antagonist lacidipine for 3 wk. Vascular albumin permeability was measured as the tissue content of i.v. injected Evans blue dye (EB) in kidney, heart, and mesenteric artery and the tissue/plasma EB ratio was calculated Systolic blood pressure was reduced by all three antihypertensive regimens. Glycemic control was similar in all **diabetic** groups. Kidney hypertrophy was not affected by any of the antihypertensive **drugs**. Hypertrophy of the mesenteric artery was enhanced by lacidipine but was not affected by **ramipril** or valsartan. Relative heart weight was also increased by lacidipine. Vascular albumin permeability, expressed as EB content in micrograms/g dry weight or as tissue/plasma EB ratio, was higher in the kidneys of lacidipine- treated rats than in any other group of **diabetic** rats. There was a pos. correlation between kidney weight/body weight and kidney/plasma EB ratio in the **diabetic** rats. These findings indicate that the dihydropyridine calcium antagonist lacidipine is associated with an unfavorable effect on vascular hypertrophy and on vascular albumin permeability in the kidneys in rats with hypertension and **diabetes** mellitus. Furthermore, there seems to be a coupling in the **diabetic** kidney between hypertrophy and increased vascular albumin permeability.

IT **87333-19-5, Ramipril**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of calcium antagonism, **angiotensin converting enzyme** inhibition, and angiotensin II-AT-receptor blockade on hypertrophy and albumin permeability in rat model combining hypertension and **diabetes** mellitus)

L16 ANSWER 62 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:426235 HCAPLUS
DOCUMENT NUMBER: 125:132132
TITLE: Kinins or nitric oxide, or both, are involved in the antitrophic effects of **angiotensin converting enzyme** inhibitors on

diabetes-associated mesenteric vascular hypertrophy in the rat
AUTHOR(S): Rumble, Jonathan R.; Komers, Radko; Cooper, Mark E.
CORPORATE SOURCE: Austin & Repatriation Medical Centre, University Melbourne, Heidelberg, 3081, Australia
SOURCE: Journal of Hypertension (**1996**), 14(5), 601-607
CODEN: JOHYD3; ISSN: 0263-6352
PUBLISHER: Rapid Science Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors determined the roles played by kinins/nitric oxide and angiotensin II in the antitrophic effects of **angiotensin converting enzyme** inhibitors on mesenteric arteries after 3 wk of streptozotocin **diabetes** by using blockers both of the angiotensin II AT1 receptor and of the bradykinin B2 receptor. Design Male **diabetic** Wistar rats were randomly allocated to receive no **treatment**, the **angiotensin converting enzyme** inhibitors perindopril or **ramipril**, the AT1 receptor blocker ZD 7155, the bradykinin B2 receptor blocker Hoe 140, the nitric oxide synthase inhibitor NG-nitro-L-arginine-Me ester, concomitant administration of perindopril plus s.c. Hoe 140, perindopril plus NG-nitro-L-arginine, or **ramipril** plus Hoe 140 (Hoe 140 administered via an Alzet mini-osmotic pump). After 3 wk, the rats were killed, their blood collected and their mesenteric vessels removed. The mesenteric vascular weight was measured and the media wall:lumen area ratio was assessed using quant. histomorphometric techniques. **Diabetes** was associated with an increase in mesenteric weight and media wall:lumen area ratio. The **angiotensin converting enzyme** inhibitors, perindopril and **ramipril**, and the AT1 receptor antagonist ZD 7155 reduced blood pressure and attenuated vascular weight and media wall:lumen area ratio. Concomitant administration of an **angiotensin converting enzyme** inhibitor with the kinin antagonist Hoe 140, administered either s.c. or via a mini-osmotic pump, or of the nitric oxide synthase inhibitor NG-nitro-L-arginine attenuated the effect of the **angiotensin converting enzyme** inhibitor on the mesenteric vascular weight and wall:lumen area ratios. **Treatment** with Hoe 140 or NG-nitro-L-arginine alone affected none of these parameters. Thus, the antitrophic effect of **angiotensin converting enzyme** inhibitors on **diabetic** mesenteric arteries is mediated by inhibition of angiotensin II and by actions on the kinin-nitric oxide pathway.

IT **87333-19-5, Ramipril**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(kinins or nitric oxide or angiotensin II are involved in antitrophic effects of **angiotensin converting enzyme** inhibitors on **diabetes**-associated mesenteric vascular hypertrophy in rat)

L16 ANSWER 63 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:426067 HCAPLUS
DOCUMENT NUMBER: 125:76029
TITLE: Effect of ramipril on insulin sensitivity in obese patients. Time-course study of glucose infusion rate during euglycemic hyperinsulinemic clamp
AUTHOR(S): Valensi, P.; Derobert, E.; Genthon, R.; Riou, J. P.
CORPORATE SOURCE: Service d'Endocrinologie-Diabetologie-Nutrition,

Hopital Jean Verdier, Bondy, 93140, Fr.
SOURCE: Diabetes & Metabolism (**1996**), 22(3), 197-200
CODEN: DIMEFW
PUBLISHER: Masson
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To assess the effects of **angiotensin converting enzyme** (**ACE**) inhibitor on insulin action in obesity, five normotensive non-**diabetic** obese women were examined on two occasions as part of a double-blind, randomized, cross-over study involving ten days of **treatment** with either 1.25 mg **ramipril** or placebo. The study consisted of a euglycemic hyperinsulinemic clamp (two periods of insulin infusion at rates of 0.4 and 1 mU/kg/min, 2 h for each step) combined with indirect calorimetry. The most notable results involved a significantly faster time-course of glucose infusion rates during the first 30 min of each insulin infusion period [analyzed by calculating slopes (S1 and S2)] after **ramipril** than placebo administration. The mean glucose infusion rates reached during the last 30 min of each insulin infusion period (G1 and G2), as well as the increases in carbohydrate oxidation rates during the clamp (C1-C0 and C2-C0) and the decreases in plasma nonesterified fatty acids (A0-A1 and A0-A2), were not significantly different after **ramipril** and placebo. According to robust principal component anal. of S1, S2, G1, G2, C1, C2, A1 and A2 (orthogonally to C0 and A0), insulin sensitivity was improved with **ramipril** as compared to placebo ($p = 0.013$). This study strongly suggests that a low dose of an **ACE** inhibitor increases the activation phase of insulin action in normotensive **nondiabetic** obese patients and may accelerate insulin action.

L16 ANSWER 64 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1996:224936 HCAPLUS
DOCUMENT NUMBER: 124:332380
TITLE: The HOPE (heart outcomes prevention evaluation) study: The design of a large, simple randomized trial of an **angiotensin converting enzyme** inhibitor (ramipril) and vitamin E in patients at high risk of cardiovascular events
AUTHOR(S): Yusuf, Salim
CORPORATE SOURCE: Hamilton General Hospital, Canadian Cardiovascular Collaboration, Hamilton, ON, L8L 2X2, Can.
SOURCE: Canadian Journal of Cardiology (**1996**), 12(2), 127-37
CODEN: CJCAEX; ISSN: 0828-282X
PUBLISHER: Pulsus Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Our objective was to describe the design of the HOPE (Heart Outcomes Prevention Evaluation) Study. Description of the key design features of HOPE, a large, simple randomized trial of two widely applicable **treatments** - **ramipril**, an **angiotensin-converting enzyme** inhibitor; and vitamin E, a naturally occurring antioxidant vitamin - in the prevention of myocardial infarction, stroke or cardiovascular death. Two-hundred and sixty-seven hospitals, physician offices and clinics in Canada, the United States, Mexico, Europe and South America. Over 9000 women and men aged 55 yr and above at high risk for cardiovascular events such as myocardial infarction and stroke were recruited over 18 mo. A 2x2 factorial design with **ramipril** and vitamin E with follow-up for up to four years. The results of HOPE will have direct public health impact and are likely to be readily incorporated into clin. practice. Key design features of HOPE are

inclusion of individuals at high risk of cardiovascular disease, inclusion of a substantial proportion of patients with **diabetes** (36%) and women (27%), and detailed substudies to provide data on mechanisms of benefit.

L16 ANSWER 65 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:525139 HCAPLUS
DOCUMENT NUMBER: 122:288148
TITLE: Acute renal hemodynamic effects of **ACE** inhibition in diabetic hyperfiltration and role of kinins
AUTHOR(S): Komers, Radko; Cooper, Mark E.
CORPORATE SOURCE: Dep. of Medicine, Univ. of Melbourne, Victoria, 3081, Australia
SOURCE: American Journal of Physiology (**1995**), 268(4, Pt. 2), F588-F594
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Angiotensin converting enzyme** (**ACE**) inhibitors not only reduced angiotensin II (ANG II) levels but also inhibit kinin degradation The relative roles of ANG II and bradykinin in the acute action of **ACE** inhibitors on renal hemodynamic parameters in rats after 3 wk of **diabetes** were explored using antagonists of the ANG II type 1 (AT1) and the bradykinin B2 receptors. Conscious control and streptozotocin **diabetic** male Sprague-Dawley rats were randomized to receive vehicle, the **ACE** inhibitor, **ramiprilat**, the B2-receptor blocker, HOE-140, the AT1-receptor blocker, valsartan, or the combination of **ramiprilat** and HOE-140. Systolic blood pressure, glomerular filtration rate (GFR), renal plasma flow (RPF), filtration fraction and urinary flow, and sodium excretion were assessed before and during **treatment.** **Diabetic** animals had higher GFR and a tendency toward increased RPF and filtration fraction compared with control animals. Acute **ramiprilat** infusion decreased GFR significantly in **diabetic** but not in control animals. Valsartan and the combination of **ramiprilat** and HOE-140 reduced blood pressure to a similar degree to **ramiprilat** alone, yet did not reduce GFR. No decrease in GFR was observed in any control rat groups. **Ramiprilat** decreased RPF in **diabetic** rats but increased RPF in control rats. No such effects on RPF were observed with valsartan. HOE-140 alone did not influence any renal parameter in the **diabetic** rats. **Diabetic** rats had increased urinary flow and sodium excretion, but these parameters were not influenced by any **drug** regimen. In summary, the effects of acute **ACE** inhibition in reducing **diabetic** hyperfiltration could be attenuated by concomitant bradykinin receptor blockade and could not be reproduced by the AT1-receptor blocker, valsartan. These findings suggest that kinins play an important role in mediating the acute renal hemodynamic effects of **ACE** inhibitors in exptl. **diabetes**

IT **87269-97-4**, **Ramiprilat**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(acute renal hemodynamic effects of **ACE** inhibition in **diabetic** hyperfiltration and role of kinins)

L16 ANSWER 66 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1994:621610 HCAPLUS
DOCUMENT NUMBER: 121:221610
TITLE: **Ramipril** prevents hypersensitivity to phenylephrine in aorta from streptozotocin-induced **diabetic** rats
AUTHOR(S): Murray, P.; Pitt, B.; Webb, R. C.
CORPORATE SOURCE: Department Physiology, University Michigan, Ann Arbor, MI, USA
SOURCE: Diabetologia (**1994**), 37(7), 664-70
CODEN: DBTGAJ; ISSN: 0012-186X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB This study investigated the protective effect of the **angiotensin converting enzyme** inhibitor, **ramipril**, on endothelium-dependent responses in arteries from control (CON) and streptozotocin-induced (STZ) **diabetic** rats. Three hypotheses were tested: (1) there is an endothelium-dependent component to the increased alpha-adrenergic responsiveness characteristic of **diabetes**; (2) endothelium-dependent, acetylcholine-induced relaxation is attenuated in aorta from **diabetic** rats; and (3) **ramipril** (3 mg/kg daily in the food, 12-15 wk) will prevent functional vascular changes in **diabetic** rats. Vascular function was assessed in aortic rings using standard muscle bath procedures for measurement of isometric force. Sensitivity to phenylephrine was increased in aortic rings from **diabetic** compared to control values , and removal of the endothelium (-Endo) increased phenylephrine sensitivity. The magnitude of the shift in responsiveness following endothelium removal was greatest in control rats. **Ramipril treatment** (Ram) partially normalized phenylephrine responsiveness in intact and denuded vessels. Vasodilation to acetylcholine and nitroglycerin was not altered in **diabetic** rats nor was it affected by **ramipril treatment**. **Diabetes** increases contractile sensitivity to phenylephrine but not to vasodilators and chronic **ramipril treatment** prevents this increase in contractile sensitivity. **Ramipril treatment** did not alter the hyperglycemic condition induced by streptozotocin. The changes in phenylephrine sensitivity appear to involve an endothelial and a smooth muscle component.

IT **87333-19-5**, **Ramipril**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**ramipril** prevention of hypersensitivity to phenylephrine in aorta from **diabetics**)

L16 ANSWER 67 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1992:543453 HCAPLUS
DOCUMENT NUMBER: 117:143453
TITLE: Use of a combination of an **ACE** (**angiotensin-converting enzyme**) inhibitor with a calcium antagonist in the treatment of proteinuria
INVENTOR(S): Becker, Reinhard; Henning, Rainer; Teetz, Volker; Urbach, Hansjoerg
PATENT ASSIGNEE(S): Hoechst A.-G., Germany
SOURCE: Eur. Pat. Appl., 22 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 488059	A2	19920603	EP 1991-119892	19911121 <--
EP 488059	A3	19921125		
EP 488059	B1	19950906		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
EP 649654	A1	19950426	EP 1994-117179	19911121 <--
EP 649654	B1	19990210		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
ES 2079545	T3	19960116	ES 1991-119892	19911121 <--
AT 176592	E	19990215	AT 1994-117179	19911121 <--
ES 2129563	T3	19990616	ES 1994-117179	19911121 <--
AU 9188117	A1	19920528	AU 1991-88117	19911126 <--
AU 655784	B2	19950112		
CA 2055948	AA	19920528	CA 1991-2055948	19911126 <--
CA 2055948	C	20021112		
NO 9104637	A	19920529	NO 1991-4637	19911126 <--
NO 311070	B1	20011008		
ZA 9109318	A	19920826	ZA 1991-9318	19911126 <--
JP 04308533	A2	19921030	JP 1991-310608	19911126 <--
HU 62468	A2	19930528	HU 1991-3674	19911126 <--
HU 219447	B	20010428		
CN 1072601	A	19930602	CN 1991-111099	19911126 <--
CN 1060679	B	20010117		
US 5236933	A	19930817	US 1991-798501	19911126 <--
SK 279626	B6	19990111	SK 1991-3587	19911126 <--
CZ 286168	B6	20000216	CZ 1991-3587	19911126 <--
KR 225997	B1	19991015	KR 1991-21370	19911127 <--
US 5366994	A	19941122	US 1993-57516	19930506 <--
CZ 286187	B6	20000216	CZ 1997-2830	19970908 <--
HK 1011927	A1	20000728	HK 1998-113023	19981209 <--
PRIORITY APPLN. INFO.:			DE 1990-4037691 A	19901127
			EP 1991-119892 A3	19911121
			CS 1991-3587 A	19911126
			US 1991-798501 A3	19911126

OTHER SOURCE(S): MARPAT 117:143453

AB An **ACE** inhibitor R3O2CCHR4NR5C(:O)CHR1NHCH(CO2R2)(CH2)nR [n = 1, 2; R = H, (substituted) aliphatic, alicyclic, aromatic, hydrocarbyl- or heterocyclyloxy or -thio; R1 = H, (substituted) hydrocarbyl or heteroarom.; R2, R3 = H, (substituted) aliphatic, alicyclic, aromatic, araliph.; R4 and R5 complete a heterocyclic mono-, bi-, or tricyclic ring system with 3-15 C atoms], combined with a Ca antagonist, is used for prevention and **therapy** of proteinuria secondary to **diabetes** mellitus, glomerulosclerosis, and loss of kidney mass. Thus, rats with 1 kidney removed and the other infarcted through ligation were administered **ramipril** (**ACE** inhibitor; 1.4 mg/kg) and felodipine (Ca antagonist; 41 mg/kg) in the feed. An increase in proteinuria from <20 to 105 mg/24 h was observed in controls, compared to only 31 mg/24 h in treated rats. Tablets were prepared containing trandolapril (**ACE** inhibitor) 3, verapamil (Ca antagonist) 50, corn starch 130, gelatin 8.0, microcryst. cellulose 2.0, and Mg stearate 2.0 g/1000.

IT **87333-19-5**, **Ramipril**
RL: BIOL (Biological study)
(proteinuria **treatment** with calcium antagonist and)

L16 ANSWER 68 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:240281 HCAPLUS
DOCUMENT NUMBER: 114:240281

TITLE: Salt blocks the renal benefits of **ramipril** in **diabetic** hypertensive rats
AUTHOR(S): Fabris, Bruno; Jackson, Bruce; Johnston, Colin I.
CORPORATE SOURCE: Dep. Med., Austin Hosp., Heidelberg, 3084, Australia
SOURCE: Hypertension (**1991**), 17(4), 497-503
CODEN: HPRTDN; ISSN: 0194-911X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To establish if the benefit of **angiotensin-converting enzyme** inhibitor **therapy** in retarding progressive **diabetic** renal injury is due to a specific intrarenal effect or the systemic hypotensive effect, the authors studied the effect of long-term **ramipril treatment** on blood pressure, glomerular filtration rate, and urinary protein excretion in streptozotocin-**diabetic** spontaneously hypertensive rats. The hypotensive effect of **ramipril** was prevented by a high-salt diet, which did not alter the degree of renal **angiotensin-converting enzyme** inhibition. Three weeks after uninephrectomy and induction of **diabetes**, rats were allocated to 3 groups. Groups 1 and 2 were given 1% NaCl, whereas group 3 was given water as drinking solution One week later, groups 2 and 3 received 0.4 mg/kg/day **ramipril** in their drinking solution, which was continued over a 2-mo period. **Ramipril** produced a blood pressure fall only in water-drinking rats (group 3) despite a similar reduction in plasma and renal **angiotensin-converting enzyme** activity in groups 2 and 3. Salt-loaded rats had a progressive increase in urinary protein excretion over the duration of study. **Ramipril treatment** prevented an increase in protein excretion only in animals given water and with a reduced systolic blood pressure. Glomerular filtration rate was similar in all 3 groups. **Ramipril treatment** improved animal survival independently of a reduction in blood pressure or an effect on proteinuria. Although it is possible that **angiotensin-converting enzyme** inhibitors have specific intrarenal effects reducing progression of **diabetic** proteinuria, concomitant control of systemic blood pressure appears to be necessary to demonstrate a benefit.

IT **87333-19-5, Ramipril**
RL: BIOL (Biological study)
(as **angiotensin-converting enzyme** inhibitor, kidney beneficial effect of, in **diabetic** hypertension, salt decrease of)

L16 ANSWER 69 OF 69 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1989:608966 HCAPLUS
DOCUMENT NUMBER: 111:208966
TITLE: **Ramipril** reduces albuminuria in **diabetic** rats fed a high-protein diet
AUTHOR(S): O'Brien, R. C.; Cooper, M. E.; Allen, T. J.; Jerums, G.
CORPORATE SOURCE: Dep. Med., Univ. Melbourne, Heidelberg, Australia
SOURCE: Clinical and Experimental Pharmacology and Physiology (**1989**), 16(8), 675-80
CODEN: CEXPB9; ISSN: 0305-1870
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Streptozotocin **diabetes** was induced in rats fed a 50% protein diet. The animals were randomized to receive either the **angiotensin-converting enzyme (ACE)** inhibitor **ramipril**, 1 mg/L in drinking water, or no **treatment** and were studied for 6 mo. **Blood**

glucose, body weight and glomerular filtration rate (GFR) were measured at 0, 1, 4, 8 and 16 wk of **diabetes**, and urinary albumin excretion was measured every 8 wk. In both groups, GFR increased within 1 wk of induction of **diabetes** and thereafter remained stable. There was no difference in GFR between the treated and untreated groups. Urinary albumin excretion increased progressively in both groups throughout the study. However, **ramipril treatment** reduced albuminuria by .apprx.50% at weeks 16 and 24. The amelioration of **diabetic** albuminuria by **ACE** inhibition, in the setting of high dietary protein intake, may have important implications for the **treatment** of human **diabetic** nephropathy.

IT **87333-19-5**, **Ramipril**
RL: RCT (Reactant); RACT (Reactant or reagent)
(albuminuria reduction by, in **diabetes** associated with high-protein diet)

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=> => d stat que
L1             5 SEA FILE=REGISTRY ABB=ON  PLU=ON  RAMIPRIL/BI
L2               SEL  PLU=ON  L1 1- CHEM :      25 TERMS
L3         71750 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L2
L4         71750 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L3 OR RAMIPRIL
L7        169837 SEA FILE=HCAPLUS ABB=ON  PLU=ON  DIABETE?/CV OR ?DIABET? OR
                 (BLD OR BLOOD)(2A)(SUGAR OR GLUCOSE)
L8           164 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L7(L)L4
L9          1934 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L4(L)(?MEDIC? OR ?DRUG? OR
                 ?PHARMA? OR ?THERAP? OR TREATMENT OR TREATING)
L10          130 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L8 AND L9
L11           77 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L10 AND PD=<OCTOBER 21, 2002
L12            8 SEA FILE=REGISTRY ABB=ON  PLU=ON  ANGIOTENSIN CONVERTING
                 ENZYME?/CN
L13              SEL  PLU=ON  L12 1- CHEM :      38 TERMS
L14          148 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L13
L15        23670 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L14 OR ANGIOTENSIN(W)CONVERTIN
                 G(W)ENZYME? OR ACE
L16           69 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L15 AND L11
L17         1994 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L15(L)L7
L22        12726 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L15(A)INHIBITOR
L25         1516 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L17 AND L22
L26        28821 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L7(L)(REDUC? OR AMEL?)
L27          807 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L25 AND L26
L28          339 SEA FILE=HCAPLUS ABB=ON  PLU=ON  REDUC?(A)?DIABE?
L29           11 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L28 AND L27
L30            9 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L29 NOT L16


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=> d ibib abs hitstr l30 1-9

L30  ANSWER 1 OF 9  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:        2005:16759  HCAPLUS
DOCUMENT NUMBER:         142:422657
TITLE:                   Prevention of type 2 diabetes mellitus through
                         inhibition of the renin-angiotensin system
AUTHOR(S):               Scheen, Andre J.
CORPORATE SOURCE:        Division of Diabetes, Department of Medicine,
                         Nutrition and Metabolic Disorders, CHU Sart Tilman,
                         Liege, Belg.
```

SOURCE: Drugs (2004), 64(22), 2537-2565
CODEN: DRUGAY; ISSN: 0012-6667
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Type 2 **diabetes** mellitus is becoming a major health problem associated with excess morbidity and mortality. As the prevalence of type 2 **diabetes** is rapidly increasing, prevention of the disease should be considered as a key objective in the near future. Besides lifestyle changes, various pharmacol. treatments have proven their efficacy in placebo-controlled clin. trials, including **antidiabetic** drugs such as metformin, acarbose and troglitazone, or antiobesity agents such as orlistat. Arterial hypertension, a clin. entity in which insulin resistance is common, is strongly associated with type 2 **diabetes** and may precede the disease by several years. While antihypertensive agents such as diuretics or β-adrenoceptor antagonists may worsen insulin resistance and impair glucose tolerance, newer antihypertensive agents exert neutral or even slightly pos. metabolic effects. Numerous clin. trials have investigated the effects of **ACE inhibitors** or angiotensin II receptor antagonists (ARAs) on insulin sensitivity in hypertensive patients, with or without **diabetes**, with no consistent results. Almost half of the studies with **ACE inhibitors** in hypertensive **nondiabetic** individuals demonstrated a slight but significant increase in insulin sensitivity as assessed by insulin-stimulated glucose disposal during a euglycemic hyperinsulinemic clamp, while the other half failed to reveal any significant change. The effects of ARAs on insulin sensitivity are neutral in most studies. Mechanisms of improvement of glucose tolerance and insulin sensitivity through the inhibition of the renin-angiotensin system (RAS) are complex. They may include improvement of blood flow and microcirculation in skeletal muscles and, thereby, enhancement of insulin and glucose delivery to the insulin-sensitive tissues, facilitating insulin signaling at the cellular level and improvement of insulin secretion by the β cells. Six recent large-scale clin. studies reported a remarkably consistent **reduction** in the incidence of type 2 **diabetes** in hypertensive patients treated with either **ACE inhibitors** or ARAs for 3-6 years, compared with a thiazide diuretic, β-adrenoceptor antagonist, the calcium channel antagonist amlodipine or even placebo. The relative risk **reduction** averaged 14% ($p = 0.034$) in the CAPPP (Captopril Prevention Project) with captopril compared with a thiazide or β1-adrenoceptor antagonist, 34% ($p < 0.001$) in the HOPE (Heart Outcomes Prevention Evaluation) study with ramipril compared with placebo, 30% ($p < 0.001$) in the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) with lisinopril compared with chlortalidone, 25% ($p < 0.001$) in the LIFE (Losartan Intervention For Endpoint **reduction** in hypertension study) with losartan compared with atenolol, and 25% ($p = 0.09$) in the SCOPE (Study on Cognition and Prognosis in the Elderly) with candesartan cilexetil compared with placebo, and 23% ($p < 0.0001$) in the VALUE (Valsartan Antihypertensive Long-term Use Evaluation) trial with valsartan compared with amlodipine. All these studies considered the development of **diabetes** as a secondary endpoint, except the HOPE trial where it was a post hoc anal. These encouraging observations led to the initiation of two large, prospective, placebo-controlled randomized clin. trials whose primary outcome is the prevention of type 2 **diabetes**: the DREAM (**Diabetes Reduction** Approaches with ramipril and rosiglitazone Medications) trial with the **ACE inhibitor** ramipril and the NAVIGATOR (Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research) trial with the ARA valsartan. Finally,

ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) will also investigate as a secondary endpoint whether it is possible to prevent the development of type 2 **diabetes** by blocking the RAS with either an **ACE inhibitor** or an ARA or a combination of both. Thus, the recent consistent observations of a 14 - 34% **reduction** of the development of **diabetes** in hypertensive patients receiving **ACE inhibitors** or ARAs are exciting. From a theor. point of view, they emphasize that there are many aspects of the pathogenesis, prevention and treatment of type 2 **diabetes** that still need to be uncovered. From a practical point of view, they may offer a new strategy to **reduce** the ongoing epidemic and burden of type 2 **diabetes.**

REFERENCE COUNT: 204 THERE ARE 204 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 2 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:363108 HCAPLUS
DOCUMENT NUMBER: 141:405885
TITLE: Peroxisome Proliferator- Activated Receptor Ligand Bezafibrate for Prevention of Type 2 Diabetes Mellitus in Patients With Coronary Artery Disease
AUTHOR(S): Tenenbaum, Alexander; Motro, Michael; Fisman, Enrique Z.; Schwammenthal, Ehud; Adler, Yehuda; Goldenberg, Ilan; Leor, Jonathan; Boyko, Valentina; Mandelzweig, Lori; Behar, Solomon
CORPORATE SOURCE: Chaim Sheba Medical Center, Cardiac Rehabilitation Institute, Neufeld Cardiac Research Institute, Tel-Hashomer, Israel
SOURCE: Circulation (2004), 109(18), 2197-2202
CODEN: CIRCAZ; ISSN: 0009-7322
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Background: Recent studies have shown that type 2 **diabetes** is preventable by both lifestyle interventions and medications that influence primary glucose metabolism Whether pharmacol. interventions that influence primary lipid metabolism can also delay development of type 2 **diabetes** is unknown. The goal of this study was to evaluate the effect of the peroxisome proliferator-activated receptor ligand bezafibrate on the progression of impaired fasting glucose phase to type 2 **diabetes** in patients with coronary artery disease over a 6.2-yr follow-up period. Methods and Results: The study sample comprised 303 **nondiabetic** patients 42 to 74 yr of age with a fasting **blood glucose** level of 110 to 125 mg/dL (6.1 to 6.9 mmol/L). The patients received either 400 mg bezafibrate retard (156 patients) or placebo (147 patients) once a day. No patients were using statins, and use of **ACE inhibitors**, which also **reduce diabetes** incidence, was relatively low. During follow-up, development of new-onset **diabetes** was recorded in 146 patients: in 80 (54.4%) from the placebo group and 66 (42.3%) from the bezafibrate group (P = 0.04). The mean time until onset of new **diabetes** was significantly delayed in patients on bezafibrate compared with patients on placebo: 4.6±2.3 vs. 3.8±2.6 yr (P = 0.004). Multivariate anal. identified bezafibrate treatment as an independent predictor of **reduced** risk of new **diabetes** development (hazard ratio, 0.70; 95% CI, 0.49 to 0.99). Other significant variables associated with future overt type 2 **diabetes** in patients with impaired fasting glucose were total cholesterol level (hazard ratio, 1.22; 95% CI 1.0 to 1.51) and body mass

index (hazard ratio, 1.10; 95% CI, 1.05 to 1.16). Conclusions: Bezafibrate **reduces** the incidence and delays the onset of type 2 **diabetes** in patients with impaired fasting glucose. Whether the combination of bezafibrate with other recommended drugs for secondary prevention (statins and **ACE inhibitors**) would be as efficacious as suggested by our results remains to be determined

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 3 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:204701 HCAPLUS
DOCUMENT NUMBER: 141:235344
TITLE: Beneficial effects of metformin on haemostasis and vascular function in man
AUTHOR(S): Grant, P. J.
CORPORATE SOURCE: Academic Unit of Molecular Vascular Medicine, Leeds School of Medicine, Leeds, UK
SOURCE: Diabetes & Metabolism (2003), 29(4, Pt. 2), 6S44-6S52 CODEN: DIMEFW; ISSN: 1262-3636
PUBLISHER: Masson Editeur
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Type 2 **diabetes** is characterized by insulin resistance in association with clustering of atherothrombotic risk factors (dysglycemia, hyperinsulinemia, hypertension, raised triglyceride, low HDL cholesterol and increased levels of plasminogen activator inhibitor-1 (PAI-1) and clotting factor VII). There is a 3-5 fold increase in risk of myocardial infarction rising to 10-20 fold in the presence of microalbuminuria and overall around 70-75% of subjects with type 2 **diabetes** die of cardiovascular disease. However, classical risk factors which associate with insulin resistance do not account for all the increased burden of vascular disease in **diabetic** subjects. Metformin is a biguanide compound which is antihyperglycemic, **reduces** insulin resistance and has cardioprotective effects on lipids, thrombosis and blood flow. Metformin has a weight neutral/weight lowering effect and **reduces** hypertriglyceridemia, elevated levels of PAI-1, factor VII and C-reactive protein. In addition recent studies indicate that metformin has direct effects on fibrin structure/function and stabilizes platelets, two important components of arterial thrombus. The United Kingdom Prospective **Diabetes** Study (UKPDS) reported that metformin was associated with a 32% **redn** . in any **diabetes** related endpoint ($p < 0.002$), a 39% **reduction** in myocardial infarction ($p < 0.01$) and a non-significant 29% fall in microvascular complications. The figures for macrovascular complications compare favorably for those described for other cardioprotective agents such as **ACE inhibitors** and statins. These findings confirm metformin as first line therapy in the management of obese insulin resistant type 2 **diabetes** and in the prevention of the vascular complications of this common condition.

REFERENCE COUNT: 83 THERE ARE 83 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 4 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:126946 HCAPLUS
DOCUMENT NUMBER: 141:166950
TITLE: Nitrosative injury and antioxidant therapy in the management of diabetic neuropathy
AUTHOR(S): Cowell, Rita M.; Russell, James W.
CORPORATE SOURCE: Department of Neurology, University of Michigan, Ann Arbor, MI, 48109-0585, USA

SOURCE: Journal of Investigative Medicine (2004), 52(1), 33-44
CODEN: JINVFI; ISSN: 1081-5589
PUBLISHER: BC Decker Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Strong evidence implicates oxidative stress as a mediator of **diabetes**-induced microvascular complications, including distal sym. polyneuropathy. Dorsal root ganglia neurons are particularly susceptible to glucose-mediated oxidative stress and die by apoptotic mechanisms in animal and cell culture models of **diabetes.** Key mediators of glucose-induced oxidative injury are superoxide anions and nitric oxide (NO). Superoxides are believed to underlie many of the oxidative changes in hyperglycemic conditions, including increases in aldose **reductase** and protein kinase C activity. Superoxides can also react with NO, forming peroxynitrite (ONOO-), which rapidly causes protein nitration or nitrosylation, lipid peroxidn., DNA (DNA) damage, and cell death. ONOO- formation is dependent on both superoxide and NO concns.; therefore, cells that constitutively express NO synthase, such as endothelial cells and neurons, may be more vulnerable to ONOO--induced cell death in conditions favoring the production of superoxides. Although NO and ONOO- can cause endothelial and neuronal cell death in vitro, in animal models of **diabetes**, **redns.** in endothelial NO production can inhibit vasodilatation and cause nerve ischemia. Therefore, ideal therapeutic approaches should limit the formation of superoxides and ONOO- while preventing **redns.** in vascular NO. Despite strong evidence that oxidative stress is associated with complications of **diabetes**, including neuropathy, the results of clin. trials of antioxidants have shown some promise but not established therapeutic efficacy. Clin. studies of several antioxidants, including α-lipoic acid, vitamins C and E, aldose **reductase** inhibitors, and growth factors, in **diabetic** neuropathy are discussed.

REFERENCE COUNT: 138 THERE ARE 138 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 5 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:319693 HCAPLUS
DOCUMENT NUMBER: 138:297672
TITLE: Method using an **angiotensin converting enzyme (ACE) inhibitor** for **reducing** type 2 **diabetes** in high risk patients
INVENTOR(S): Yusuf, Salim
PATENT ASSIGNEE(S): Aventis Pharma Deutschland G.m.b.H., Germany
SOURCE: PCT Int. Appl., 18 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003032963	A2	20030424	WO 2002-EP11636	20021017
WO 2003032963	A3	20031224		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,

UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2463682	AA	20030424	CA 2002-2463682	20021017
EP 1438043	A2	20040721	EP 2002-790295	20021017
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
US 2005065203	A1	20050324	US 2004-492919	20041110
PRIORITY APPLN. INFO.:			US 2001-344495P P	20011017
			WO 2002-EP11636 W	20021017

AB The invention discloses a method of **reducing diabetes** in patients who are at risk for developing **diabetes** comprising administering an effective amount of an **ACE inhibitor** for sufficient period to prevent the development of **diabetes.** Also disclosed is a method for slowing or reversing the decline of β-cell function in an individual comprising administering an effective amount of an **angiotensin converting enzyme inhibitor** for a sufficient period to prevent the decline of β-cell function. The invention also discloses a method of increasing islet blood flow in an individual comprising administering an effective amount of an **angiotensin converting enzyme inhibitor** for a sufficient period to increase islet blood flow. Further disclosed are methods for increasing pancreatic β-cell perfusion and for lowering aldosterone secretion and renal potassium wasting. The invention further discloses the use of an **ACE inhibitor** or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament for the prevention or **redn** . of the onset of **diabetes** in patients who are at risk for developing **diabetes**, for the prevention, slowing or reversing the decline of β-cell function, for increasing islet blood flow, for increasing pancreatic β-cell perfusion, and for lowering aldosterone secretion and renal potassium wasting. The **ACE inhibitor** is e.g. ramipril.

L30 ANSWER 6 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:161322 HCAPLUS
DOCUMENT NUMBER: 139:285990
TITLE: Enalapril **Reduces** the Incidence of **Diabetes** in Patients With Chronic Heart Failure: Insight from the studies of left ventricular dysfunction (SOLVD)
AUTHOR(S): Vermes, Emmanuelle; Ducharme, Anique; Bourassa, Martial G.; Lessard, Myriam; White, Michel; Tardif, Jean-Claude
CORPORATE SOURCE: Department of Medicine, Montreal Heart Institute, Montreal, QC, H1T 1C8, Can.
SOURCE: Circulation (2003), 107(9), 1291-1296
CODEN: CIRCAZ; ISSN: 0009-7322
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Diabetes** mellitus is a predictor of morbidity and mortality in patients with heart failure. The effect of **angiotensin-converting enzyme (ACE) inhibitors** on the prevention of **diabetes** in patients with left ventricular dysfunction is unknown. The aim of this retrospective study was to assess the effect of the **ACE inhibitor** enalapril on the incidence of **diabetes** in the group of patients from the Montreal

Heart Institute enrolled in the Studies of Left Ventricular Dysfunction (SOLVD). Clin. charts were evaluated for fasting plasma glucose (FPG) levels by blinded reviewers. A diagnosis of **diabetes** was made when a FPG 126 mg/dL (7 mmol/L) was found at 2 visits (follow-up, 2.91.0 yr). Of the 391 patients enrolled at the Montreal Heart Institute, 291 were not **diabetic** (FPG <126 mg/dL without a history of **diabetes**), 153 of these were on enalapril and 138 were on placebo. Baseline characteristics were similar in the 2 groups. Forty patients developed **diabetes** during follow-up, 9 (5.9%) in the enalapril group and 31 (22.4%) in the placebo group (P<0.0001). By multivariate anal., enalapril remained the most powerful predictor for risk **reduction** of developing **diabetes** (hazard ratio, 0.22; 95% confidence intervals, 0.10 to 0.46; P<0.0001). The effect of Enalapril was striking in the subgroup of patients with impaired FPG (110 mg/dL [6.1 mmol/L] FPG <126 mg/dL) at baseline:1 patient (3.3%) in the enalapril group vs. 12 (48.0%) in the placebo group developed **diabetes** (P<0.0001). Enalapril significantly **reduces** the incidence of **diabetes** in patients with left ventricular dysfunction,especially those with impaired FPG.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 7 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:751196 HCAPLUS
DOCUMENT NUMBER: 135:40756
TITLE: **Angiotensin converting enzyme** inhibition **reduces** retinal overexpression of vascular endothelial growth factor and hyperpermeability in experimental **diabetes**
AUTHOR(S): Gilbert, R. E.; Kelly, D. J.; Cox, A. J.; Wilkinson-Berka, J. L.; Rumble, J. R.; Osicka, T.; Panagiotopoulos, S.; Lee, V.; Hendrich, E. C.; Jerums, G.; Cooper, M. E.
CORPORATE SOURCE: Department of Medicine (Austin and Repatriation Medical Centre) Victoria, University of Melbourne Department of Medicine, Australia
SOURCE: Diabetologia (2000), 43(11), 1360-1367
CODEN: DBTGAJ; ISSN: 0012-186X
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Angiotensin converting enzyme** (**ACE**) inhibition was recently suggested to have retinoprotective actions in **diabetic** patients but the mechanism of this effect is not known. In vitro, angiotensin II stimulates expression of vascular endothelial growth factor (VEGF), a permeability-inducing and endothelial cell specific angiogenic factor which was implicated in the pathogenesis of **diabetic** retinopathy in humans and in exptl. animals. The authors sought to determine the effects of **ACE** inhibition on retinal VEGF expression and permeability in exptl. **diabetic** retinopathy. Streptozotocin-induced **diabetic** rats and control animals were assigned at random to receive **ACE inhibitor** treatment or vehicle. At 24 wk the retinal VEGF protein gene expression was assessed by Northern blot anal. and in situ hybridization. Retinal permeability to albumin was measured using a double isotope technique. Exptl. **diabetes** was associated with cell specific 2- to 4-fold increase in retinal VEGF protein gene expression and a 2-fold increase in retinal vascular permeability to albumin. The localization of VEGF expression in the retina was not altered in animals with exptl. **diabetes**. **Angiotensin converting**

enzyme inhibitor treatment of **diabetic** rats **reduced diabetes**-associated changes in VEGF gene expression and vascular permeability. These findings implicate the renin-angiotensin system in the VEGF overexpression and hyperpermeability which accompany **diabetic** retinopathy and provide a potential mechanism for the beneficial effects of **ACE** inhibition in **diabetic** retinal disease.

REFERENCE COUNT: 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 8 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1999:192887 HCAPLUS

TITLE: The blood vessel, linchpin of diabetic lesions

AUTHOR(S): Plante, Gerard E.; Alfred, Jude; Chakir, Mouna

CORPORATE SOURCE: Departments of Medicine (Nephrology) and Pharmacology, University of Sherbrooke, Sherbrooke, QC, Can.

SOURCE: Metabolism, Clinical and Experimental (1999), 48(3), 406-409
CODEN: METAAJ; ISSN: 0026-0495

PUBLISHER: W. B. Saunders Co.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The morbidity and mortality associated with **diabetes** mellitus are essentially related to the vascular lesions that develop over time in this condition. Both the macrocirculation and microcirculation are involved, and as a consequence, vital organs such as the brain, retina, heart, and kidney and the limbs become damaged. Because microalbuminuria represents the earliest and probably most sensitive indication of endothelial dysfunction in **diabetes** mellitus, the results of pharmacol. intervention with **angiotensin-converting enzyme inhibitors**, which treat glomerular hypertension were the first indication of potential beneficial effects in **reducing diabetic** nephroplasty. The nature of endothelial dysfunction related to **diabetes** is probably not homogeneous, since microcirculation networks are affected at different periods and with variable intensity. This appears to be the case for the aorta, the heart, segments of the digestive tract, the skin, and the skeletal muscle, the largest consumer of insulin. Although the aorta and large arteries contain a small portion of the total blood volume, their distribution of blood flow (pulse pressure) to peripheral organs may affect endothelial function in the microcirculation. Changes in the structure of conduit arteries, partly responsible for the alteration in compliance characteristics, could well be related to the way these arteries are fed by the vasa vasorum system. This report describes a new in vitro approach to examine capillary permeability in normal and alloxan-induced **diabetic** rabbits. Preliminary results indicate that the size of terminal arterioles of the vasa vasorum (increased diameter) and the capillary permeability to albumin (markedly enhanced) in this specialized network are profoundly affected in the thoracic aorta obtained from **diabetic** animals. Albumin extravasation into the interstitial fluid compartment of the aorta is likely to lead to structural and physicochem. changes: in fact, removal of interstitial macromols. via lymphatic drainage is poor in the blood vessel wall of large arteries. This exptl. approach is likely to be useful in the exploration of medications affecting the structure and function of conduit vessels.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 9 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1995:729261 HCAPLUS
DOCUMENT NUMBER: 123:132358
TITLE: **Angiotensin-converting enzyme** inhibition **reduces diabetes**-induced vascular hypertrophy: morphometric studies
AUTHOR(S): Vranes, Dimitria; Cooper, Mark E.; Dilley, Rodney J.
CORPORATE SOURCE: Heidelberg Repatriation Hospital, University of Melbourne, West Heidelberg, Australia
SOURCE: Journal of Vascular Research (1995), 32(3), 183-9
CODEN: JVREE9; ISSN: 1018-1172
PUBLISHER: Karger
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Angiotensin-converting enzyme** (**ACE**) activity and vascular mass are both increased in the mesenteric arteries of **diabetic** rats. As vascular hypertrophy may result from smooth muscle growth following increased formation of angiotensin II, we have examined the histol. nature of the increase in mesenteric arterial mass and the role of elevated **ACE** activity in **diabetic** vascular hypertrophy by administration of an **ACE inhibitor** (perindopril). Crosssectional area of the media was measured in perfusion-fixed mesenteric vessels of **diabetic** rats 3 wk after streptozotocin injection. The media was significantly larger (63%) in mesenteric vessels of **diabetic** rats compared to age-matched control animals. Medial hypertrophy in these vessels was not associated with increased blood pressure or plasma renin activity but there was evidence for increased hemodynamic load due to hyperphagia and intestinal enlargement. Increased mesenteric **ACE** activity was involved in this process as there was significant inhibition of medial hypertrophy by perindopril. Other markers of cardiovascular hypertrophy such as left ventricular weight and aortic medial area were less affected, but increased in the **diabetic** group when corrected for significant body weight effects, consistent with a systemic influence of **diabetes** on cardiovascular mass. These data provide new insights into the mechanisms of vascular complications of **diabetes** and may have implications for the use of **ACE inhibitors** in preventing or arresting **diabetes**-associated vascular pathol.

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